410 Rec'd PCT/PTO 02 OCT 2000

FORM-PTO-1390 (Rev. 10-96) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER 003300-685
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5) 09/647544
INTERNATIONAL APPLICATION NO. PCT/SE99/00544	INTERNATIONAL FILING DATE 31 March 1999	PRIORITY DATE CLAIMED 2 April 1998 and 28 January 1999
TITLE OF INVENTION AN INTEGRIN HETERODIMER AND A SUBUNIT THEREOF		
APPLICANT(S) FOR DO/EO/US EVY LUNDGREN-ÅKERLUND		

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

O I P E JC68 OCT 02 2000 PATENT & TRADEMARK OFFICE

It is contemplated that this Application be prosecuted while using Claims 1 to 134 that were presented on May 29, 2000 during the international phase of prosecution as amended in the Preliminary Amendment filed herewith.

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and the PCT Articles 22 and 39(1).
4. ☐ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US)
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). (signed Declaration will follow)
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information:

Copies of Swedish Application No. 9801164-6, filed 2 April 1998 and Swedish Application No. 9900319-6, filed 28 January 1999 were submitted during the international phase of prosecution. Thus, the claim for priority has been substantiated.

This Application qualifies for small entity status.

528 Rec'd PCT/PTO 02 OCT 2000

U.S. APPLICATION NO (If known, see 37 C.F.R. 1.50) 09/647544	INTERNATIONAL APPLICATION NO. PCT/SE99/00544	ATTORNEY'S DOCKET NUMBER 003300-685

17. [X] The following fees are submitted:				CALCULATIONS	PTO USE ONLY
Basic National Fee (37 CFR 1.492(a)(1)-(5)): Search Report has been prepared by the EPO or JPO .... $860.00 (970) International preliminary examination fee paid to USPTO (37 CFR 1.482) ...... $690.00 (956) No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) .... $710.00 (958) Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to U.S. PATENT AND TRADEMARK OFFICE $1,000.00 (960) International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) $100.00 (962)					
ENTER APPROPRIATE BASIC FEE AMOUNT =				$ 1,000.00	
Surcharge of **$130.00 (154)** for furnishing the oath or declaration later than 20 [ ] 30 [ ] months from the earliest claimed priority date (37 CFR 1.492(e)).				$ --	
Claims	Number Filed	Number Extra	Rate		
Total Claims	134 -20 =	114	X$18.00 (966)	$ 2,052.00	
Independent Claims	38 -3 =	35	X$80.00 (964)	$ 2,800.00	
Multiple dependent claim(s) (if applicable)			+ $270.00 (968)	$ --	
TOTAL OF ABOVE CALCULATIONS =				$ 5,852.00	
Reduction for 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				$ 2,926.00	-
SUBTOTAL =				$ 2,926.00	
Processing fee of **$130.00 (156)** for furnishing the English translation later than 20 [ ] 30 [ ] months from the earliest claimed priority date (37 CFR 1.492(f)). +				$ --	
TOTAL NATIONAL FEE =				$ 2,926.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00 (581)** per property +				$ --	
TOTAL FEES ENCLOSED =				$ 2,926.00	
				Amount to be: refunded	$
				charged	$

a. [X] A check in the amount of $ 2,926.00 to cover the above fees is enclosed.

b. [ ] Please charge my Deposit Account No. 02-4800 in the amount of $______ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 02-4800. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Benton S. Duffett, Jr.
BURNS, DOANE, SWECKER & MATHIS, L.L.P.
P.O. Box 1404
Alexandria, Virginia 22313-1404

Filed: October 2, 2000

Benton S. Duffett Jr.
SIGNATURE

Benton S. Duffett, Jr.
NAME

22,030
REGISTRATION NUMBER

528 Rec'd PCT/PTO 02 OCT 2000

FORM-PTO-1390 (Rev. 10-96) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER 003300-685
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5) 09/647544
INTERNATIONAL APPLICATION NO. PCT/SE99/00544	INTERNATIONAL FILING DATE 31 March 1999	PRIORITY DATE CLAIMED 2 April 1998 and 28 January 1999

TITLE OF INVENTION
AN INTEGRIN HETERODIMER AND A SUBUNIT THEREOF

APPLICANT(S) FOR DO/EO/US
EVY LUNDGREN-ÅKERLUND

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

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This Application qualifies for small entity status.

528 Rec'd PCT/PTO 02 OCT 2000

U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.50) 09/647544	INTERNATIONAL APPLICATION NO. PCT/SE99/00544	ATTORNEY'S DOCKET NUMBER 003300-685

17. [X] The following fees are submitted:	CALCULATIONS	PTO USE ONLY
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ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 1,000.00	
Surcharge of **$130.00 (154)** for furnishing the oath or declaration later than 20 [ ] 30 [ ] months from the earliest claimed priority date (37 CFR 1.492(e)).	$ --	

Claims	Number Filed	Number Extra	Rate		
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Independent Claims	38 -3 =	35	X$80.00 (964)	$ 2,800.00	
Multiple dependent claim(s) (if applicable)			+$270.00 (968)	$ --	
TOTAL OF ABOVE CALCULATIONS =				$ 5,852.00	
Reduction for 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				$ 2,926.00	-
SUBTOTAL =				$ 2,926.00	
Processing fee of **$130.00 (156)** for furnishing the English translation later than 20 [ ] 30 [ ] months from the earliest claimed priority date (37 CFR 1.492(f)). +				$ --	
TOTAL NATIONAL FEE =				$ 2,926.00	
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TOTAL FEES ENCLOSED =				$ 2,926.00	
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SEND ALL CORRESPONDENCE TO:

Benton S. Duffett, Jr.
BURNS, DOANE, SWECKER & MATHIS, L.L.P.
P.O. Box 1404
Alexandria, Virginia 22313-1404

Filed: October 2, 2000

Benton S. Duffett, Jr.
SIGNATURE

Benton S. Duffett, Jr.
NAME

22,030
REGISTRATION NUMBER

09/647544

528 Rec'd PCT/PTO 02 OCT 2000

Patent
Attorney's Docket No. 003300-685

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	BOX PCT Attention: DO/EO/US
EVY LUNDGREN-ÅKERLUND	
Application No.: Unassigned	Group Art Unit: Unassigned
Filed: October 2, 2000	Examiner: Unassigned
For: AN INTEGRIN HETERODIMER AND A SUBUNIT THEREOF	

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This application corresponds to International Application No. PCT/SE99/00544, filed March 31, 1999.

It is contemplated that this Application be prosecuted while using Claims 1 to 134 that were submitted on May 29, 2000 during the international phase of prosecution as further amended herein.

In the Abstract:

Please add the Abstract of the Disclosure that is provided on a separate sheet.

In the Claims:

Claim 8, lines 1 and 2, delete "in any one of claims 6 and 7" and insert --claim 6--.

Claim 20, line 1, delete "or 19".

Claim 21, line 1, delete "or 19".

Claim 26, line 2, delete "any one of claims 22-25" and insert --claim 22--.

Claim 27, lines 2 and 3, delete "any one of claims 22-25" and insert --claim 22--.

Claim 28, line 3, delete "any one of claims 22-25" and insert --claim 22--.

Claim 38, lines 1 and 2, delete "any one of claims 31-37" and insert --claim 31--.

Claim 41, lines 1 and 2, delete "any one of claims 31-37" and insert --claim 31--.

Claim 42, lines 1 and 2, delete "any one of claims 31-37" and insert --claim 31--.

Claim 43, lines 1 and 2, delete "any one of claims 31-37" and insert --claim 31--.

Claim 44, lines 1 and 2, delete "any one of claims 31-37" and insert --claim 31--.

Claim 45, line 1, delete "any one of claims 31-37 and insert --claim 31--.

Claim 52, lines 1 and 2, delete "any one of claims 46-51" and insert --claim 46--.

Claim 53, lines 1 and 2, delete "any one of claims 46-51" and insert --claim 46--.

Claim 60, lines 1 and 2, delete "any one of claims 54-59" and insert --claim 54--.

Claim 72, lines 1 and 2, delete "any one of claims 64-71" and insert --claim 64--.

Claim 93, line 1, delete "any one of claims 86-92" and insert --claim 86--.

Claim 96, line 1, delete "any one of claims 86-92" and insert --claim 86--.

Claim 97, line 1, delete "any one of claims 86-92" and insert --claim 86--.

Claim 98, line 1, delete "any one of claims 86-92" and insert --claim 86--.

Claim 105, lines 1 and 2, delete "any one of claims 99-104" and insert --claim 99--.

Claim 106, lines 1 and 2, delete "any one of claims 99-104" and insert --claim 99--.

Claim 113, lines 1 and 2, delete "any one of claims 107-112" and insert --claim 107--.

Claim 125, lines 1 and 2, delete "any one of claims 117-124" and insert --claim 117--.

REMARKS

The present Amendment adds an Abstract of the Disclosure on a separate sheet and eliminates the use of multiple dependency.

The examination and allowance of the application are respectfully requested.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: Benton S. Duffett, Jr.

Benton S. Duffett, Jr.
Registration No. 22,030

P.O. Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620

Date: October 2, 2000

Abstract of the Disclosure

A recombinant or isolated integrin heterodimer comprising a novel subunit $\alpha 10$ in association with a subunit β is described. The $\alpha 10$ integrin may be purified from bovine chondrocytes on a collagen-type-II affinity column. The integrin or the subunit $\alpha 10$ can be used as marker or target of all types of cells, e.g. of chondrocytes, osteoblasts and fibroblasts. The integrin or subunit $\alpha 10$ thereof can be used as marker or target in different physiological or therapeutic methods. They can also be used as active ingredients in pharmaceutical compositions and vaccines.

PTO/PCT Rec'd 26 OCT 2000
09/647544

Patent

Attorney's Docket No. 003300-685

Applicant or Patentee: EVY LUNDGREN-ÅKERLUND

Application or Patent No.: ____________

Filed or Issued: October 26, 2000

For: AN INTEGRIN HETERODIMER AND A SUBUNIT THEREOF

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS (37 C.F.R. §§ 1.9(f) AND 1.27(c)) - SMALL BUSINESS CONCERN

I hereby declare that I am

[X] the owner of the small business concern identified below:
[ ] an official of the small business concern empowered to act on behalf of the concern identified below:

NAME OF CONCERN CARTELA AB

ADDRESS OF CONCERN c/o Evy Lundgren-Åkerlund
Trollsjövägen 165, 237 33 Bjärred, Sweden

I hereby declare that the above-identified small business concern qualifies as a small business concern as defined in 13 C.F.R. § 121.12, and reproduced in 37 C.F.R. § 1.9(d), for purposes of paying reduced fees under Sections 41(a) and 41(b) of Title 35, United States Code, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average, over the previous fiscal year of the concern, of the persons employed on a full-time, part-time, or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party or parties controls or has the power to control both.

I hereby declare that rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the invention entitled An integrin heterodimer and a subunit thereof by inventor(s) Evy Lundgren-Åkerlund described in

[ ] the specification filed herewith
[X] Application No. PCT/SE99/00544, filed 31 March 1999
[ ] Patent No. ____________, issued ____________.

If the rights held by the above-identified small business concern are not exclusive, each individual, concern, or organization having rights to the invention is listed below,* and no rights to the invention are held by any person, other than the inventor, who would not qualify as an independent inventor under 37 C.F.R. § 1.9(c), or by any concern that would not qualify as either a small business concern under 37 C.F.R. § 1.9(d) or a nonprofit organization under 37 C.F.R. § 1.9(e).

*NOTE: Separate verified statements are required from each named person, concern, or organization having rights to the invention averring to their status as small entities. (37 C.F.R. § 1.27.)

(1/96)

Application Serial No. ____________
Attorney's Docket No. 003300-685

NAME ____

ADDRESS ____

[ ] individual [ ] small business concern [ ] nonprofit organization

NAME ____

ADDRESS ____

[ ] individual [ ] small business concern [ ] nonprofit organization

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earlier of the issue fee and any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 C.F.R. § 1.28(b).)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code; and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING EVY LUNDGREN-ÅKERLUND

TITLE OF PERSON OTHER THAN OWNER MANAGING DIRECTOR

ADDRESS OF PERSON SIGNING Trollsjövägen 165
237 33 BJÄRRED, SWEDEN

SIGNATURE Evy Lundgren-Åkerlund DATE 2000-10-09

(1/96)

AN INTEGRIN HETERODIMER AND A SUBUNIT THEREOF

FIELD OF THE INVENTION

The present invention relates to a recombinant or isolated integrin heterodimer comprising a subunit α10 and a subunit β, the subunit α10 thereof, homologues and fragments of said integrin and of said subunit α10 having similar biological activity, processes of producing the same, polynucleotides and oligonucleotides encoding the same, vectors and cells comprising the same, binding entities binding specifically to the same, and the use of the same.

BACKGROUND OF THE INVENTION

The integrins are a large family of transmembrane glycoproteins that mediate cell-cell and cell-matrix interactions (1-5). All known members of this superfamily are non-covalently associated heterodimers composed of an α- and a β-subunit. At present, 8 β-subunits (β1-β8) (6) and 16 α-subunits (α1-α9, αv, αM, αL, αX, αIIb, αE and αD) have been characterized (6-21), and these subunits associate to generate more than 20 different integrins. The β1-subunit has been shown to associate with ten different α-subunits, α1-α9 and αv, and to mediate interactions with extracellular matrix proteins such as collagens, laminins and fibronectin. The major collagen binding integrins are α1β1 and α2β1 (22-25). The integrins α3β1 and α9β1 have also been reported to interact with collagen (26,27) although this interaction is not well understood (28). The extracellular N-terminal regions of the α and β integrin subunits are important in the binding of ligands (29,30). The N-terminal region of the α-subunits is composed of a seven-fold repeated sequence (12,31) containing FG and GAP consensus sequences. The repeats are predicted to fold into a β-propeller domain

(32) with the last three or four repeats containing putative divalent cation binding sites. The α-integrin subunits α1, α2, αD, αE, αL, αM and αX contain a ~200 amino acid inserted domain, the I-domain (A-domain), which shows similarity to sequences in von Willebrand factor, cartilage matrix protein and complement factors C2 and B (33,34). The I-domain is localized between the second and third FG-GAP repeats, it contains a metal ion-dependent adhesion site (MIDAS) and it is involved in binding of ligands (35-38).

Chondrocytes, the only type of cells in cartilage, express a number of different integrins including α1β1, α2β1, α3β1, α5β1, α6β1, αvβ3, and αvβ5 (39-41). It has been shown that α1β1 and α2β1 mediate chondrocyte interactions with collagen type II (25) which is one of the major components in cartilage. It has also been shown that α2β1 is a receptor for the cartilage matrix protein chondroadherin (42).

SUMMARY OF THE INVENTION

The present invention relates to a novel collagen type II binding integrin, comprising a subunit α10 in association with a subunit β, especially subunit β1, but also other β-subunits may be contemplated. In preferred embodiments, this integrin has been isolated from human or bovine articular chondrocytes, and human chondrosarcoma cells.

The invention also encompasses integrin homologues of said integrin, isolated from other species, such as bovine integrin heterodimer comprising a subunit α10 in association with a subunit β, preferably β1, as well as homologues isolated from other types of human cells or from cells originating from other species.

The present invention relates in particular to a recombinant or isolated integrin subunit α10 comprising the amino acid sequence shown in SEQ ID No. 1 or SEQ ID No. 2, and homologues and or fragments thereof having the

same biological activity.

The invention further relates to a process of producing a recombinant integrin subunit α10 comprising the amino acid sequence shown in SEQ ID No. 1 or SEQ ID No. 2, or homologues or fragments thereof having similar biological activity, which process comprises the steps of

a) isolating a polynucleotide comprising a nucleotide sequence coding for a integrin subunit α10, or homologues or fragments thereof having similar biological activity,

b) constructing an expression vector comprising the isolated polynucleotide,

c) transforming a host cell with said expression vector,

d) culturing said transformed host cell in a culture medium under conditions suitable for expression of integrin subunit α10, or homologues or fragments thereof having similar biological activity, in said transformed host cell, and, optionally,

e) isolating the integrin subunit α10, or homologues or fragments thereof having the same biological activity, from said transformed host cell or said culture medium.

The integrin subunit α10, or homologues or fragments thereof having the same biological activity, can also be provided by isolation from a cell in which they are naturally present.

The invention also relates to an isolated polynucleotide comprising a nucleotide coding for a integrin subunit α10, or homologues or fragments thereof having similar biological activity, which polynucleotide comprises the nucleotide sequence shown in SEQ ID No. 1 or SEQ ID No. 2, or parts thereof.

The invention further relates to an isolated polynucleotide or oligonucleotide which hybridises to a DNA or RNA encoding an integrin subunit α10, having the amino acid sequence shown in SEQ ID No. 1 or SEQ ID No. 2, or homologues or fragments thereof, wherein said polyoligo-

nucleotide or oligonucleotide fails to hybridise to a DNA or RNA encoding the integrin subunit α1.

The invention relates in a further aspect to vectors comprising the above polynucleotides, and to cells containing said vectors and cells that have polynucleotides or oligonycleotides as shown in SEQ ID No. 1 or 2 integrated in their genome.

The invention also relates to binding entities having the capability of binding specifically to the integrin subunit α10 or to homologues or fragments thereof, such as proteins, peptides, carbohydrates, lipids, natural ligands, polyclonal antibodies or monoclonal antibodies.

In a further aspect, the invention relates to a recombinant or isolated integrin heterodimer comprising a subunit α10 and a subunit β, in which the subunit α10 comprises the amino acid sequence shown in SEQ ID No. 1 or SEQ ID No. 2, or homologues or fragments thereof having similar biological activity.

In a preferred embodiment thereof, the subunit β is β1.

The invention also relates to a process of producing a recombinant integrin heterodimer comprising a subunit α10 and a subunit β, in which the subunit α10 comprises the amino acid sequence shown in SEQ ID No. 1 or SEQ ID No. 2, which process comprises the steps of

a) isolating one polynucleotide comprising a nucleotide sequence coding for a subunit α10 of an integrin heterodimer and, optionally, another polynucleotide comprising a nucleotide sequence coding for a subunit β of an integrin heterodimer, or for homologues or fragments thereof having similar biological activity,

b) constructing an expression vector comprising said isolated polynucleotide coding for said subunit α10 in combination with an expression vector comprising said isolated nucleotide coding for said subunit β,

c) transforming a host cell with said expression vectors,

d) culturing said transformed host cell in a culture medium under conditions suitable for expression of an integrin heterodimer comprising a subunit α10 and a subunit β, or homologues or fragments thereof similar biological activity, in said transformed host cell, and, optionally,

e) isolating the integrin heterodimer comprising a subunit α10 and a subunit β, or homologues or fragments thereof having the same biological activity, from said transformed host cell or said culture medium.

The integrin heterodimer, or homologues or fragments thereof having similar biological activity, can also be provided by isolation from a cell in which they are naturally present.

The invention further relates to a cell containing a first vector, said first vector comprising a polynucleotide coding for a subunit α10 of an integrin heterodimer, or for homologues or parts thereof having similar biological activity, which polynucleotide comprises the nucleotide sequence shown in SEQ ID No. 1 or SEQ ID No. 2 or parts thereof, and, optionally, a second vector, said second vector comprising a polynucleotide coding for a subunit β of an integrin heterodimer, or for homologues or fragments thereof.

In still another aspect, the invention relates to binding entities having the capability of binding specifically to the integrin heterodimer comprising a subunit α10 and a subunit β, or to homologues or fragments thereof having similar biological activity, preferably wherein the subunit β is β1. Preferred binding entities are proteins, peptides, carbohydrates, lipids, natural ligands, polyclonal antibodies and monoclonal antibodies.

In a further aspect, the invention relates to a fragment of the integrin subunit α10, which fragment is a peptide chosen from the group comprising peptides of

the cytoplasmic domain, the I-domain and the spliced domain.

In one embodiment, said fragment is a peptide comprising the amino acid sequence KLGFFAHKKIPEEEKREEKLEQ.

In another embodiment, said fragment comprises the amino acid sequence from about amino acid no. 952 to about amino acid no. 986 of SEQ ID No. 1.

In a further embodiment, said fragment comprises the amino acid sequence from about amino acid No. 140 to about amino acid No. 337 in SEQ ID No. 1.

Another embodiment of the invention relates to a polynucleotide or oligonucleotide coding for a fragment of the human integrin subunit α10. In one embodiment this polynucleotide of oligonucleotide codes for a fragment which is a peptide chosen from the group comprising peptides of the cytoplasmic domain, the I-domain and the spliced domain. In further embodiments the polynucleotide or oligonucleotide codes for the fragments defined above.

The invention also relates to binding entities having the capability of binding specifically to a fragment of the integrin subunit α10 as defined above.

The invention also relates to a process of using an integrin subunit α10 comprising the amino acid sequence shown in SEQ ID No. 1 or SEQ ID No. 2, or an integrin heterodimer comprising said subunit α10 and a subunit β, or a homologue or fragment of said integrin or subunit having similar biological activity, as a marker or target molecule of cells or tissues expressing said integrin subunit α10, which cells or tissues are of animal including human origin.

In an embodiment of this process the fragment is a peptide chosen from the group comprising peptides of the cytoplasmic domain, the I-domain and the spliced domain.

In further embodiments of said process the fragment is a peptide comprising the amino acid sequence KLGFFAHKKIPEEEKREEKLEQ, or a fragment comprising the amino acid sequence from about amino acid No. 952 to

about amino acid No. 986 of SEQ ID No. 1, or a fragment comprising the amino acid sequence from about amino acid no. 140 to about amino acid no. 337 of SEQ ID no. 1.

The subunit β is preferably β1. The cells are preferably chosen from the group comprising chondrocytes, smooth muscle cells, endothelial cells, osteoblasts and fibroblasts.

Said process may be used during pathological conditions involving said subunit α10, such as pathological conditions comprising damage of cartilage, or comprising trauma, rheumatoid arthritis and osteoarthritis.

Said process may be used for detecting the formation of cartilage during embryonal development, or for detecting physiological or therapeutic reparation of cartilage.

Said process may also be used for selection and analysis, or for sorting, isolating or purification of chondrocytes.

A further embodiment of said process is a process for detecting regeneration of cartilage or chondrocytes during transplantation of cartilage or chondrocytes.

A still further embodiment of said process is a process for in vitro studies of differentiation of chondrocytes.

The invention also comprises a process of using binding entities having the capability of binding specifically to an integrin subunit α10 comprising the amino acid sequence shown in SEQ ID No. 1 or SEQ ID No. 2, or an integrin heterodimer comprising said subunit α10 and a subunit β, or to homologues or fragments thereof having similar biological activity, as markers or target molecules of cells or tissues expressing said integrin subunit α10, which cells or tissues are of animal including human origin.

The fragment in said process may be a peptide chosen from the group comprising peptides of the cytoplasmic domain, the I-domain and the spliced domain. In preferred embodiments said fragment is a peptide comprising the

amino acid sequence KLGFFAHKKIPEEEKREEKLEQ, or a fragment comprising the amino acid sequence from about amino acid No. 952 to about amino acid No. 986 of SEQ ID No. 1, or a fragment comprising the amino acid sequence from about amino acid No. 140 to about amino acid no. 337 of SEQ ID No. 1.

The process may also be used for detecting the presence of an integrin subunit α10 comprising the amino acid sequence shown in SEQ ID No. 1 or SEQ ID No. 2, or of an integrin heterodimer comprising said subunit α10 and a subunit β, or of homologues or fragments thereof having similar biological activity.

In a further embodiment said process is a process for determining the differentiation-state of cells during embryonic development, angiogenesis, or development of cancer.

In a still further embodiment this process is a process for detecting the presence of an integrin subunit α10, or of a homologue or fragment of said integrin subunit having similar biological activity, on cells, whereby a polynucleotide or oligonucleotide chosen from the group comprising a polynucleotide or oligonucleotide chosen from the nucelotide sequence shown in SEQ ID No. 1 is used as a marker under hybridisation conditions wherein said polynucleotide or oligonucleotide fails to hybridise to a DNA or RNA encoding an integrin subunit α1. Said cells may be chosen from the group comprising chondrocytes, smooth muscle cells, endothelial cells, osteoblasts and fibroblasts. Said integrin fragment may be a peptide chosen from the group comprising peptides of the cytoplasmic domain, the I-domain and the spliced domain, such as a peptide comprising the amino acid sequence KLGFFAHKKIPEEEKREEKLEQ, or a fragment comprising the amino acid sequence from about amino acid no. 952 to about amino acid no. 986 of SEQ ID No. 1, or a fragment comprising the amino acid sequence from about amino acid No. 140 to about amino acid no. 337 of SEQ ID No. 1.

In a still further embodiment the process is a process for determining the differentiation-state of cells during development, in pathological conditions, in tissue regeneration or in therapeutic and physiological reparation of cartilage. The pathological conditions may be any pathological conditions involving the integrin subunit α10, such as rheumatoid arthritis, osteoarthrosis or cancer. The cells may be chosen from the group comprising chondrocytes, smooth muscle cells, endothelial cells, osteoblasts and fibroblasts.

The invention also relates to a process for determining the differentiation-state of cells during development, in pathological conditions, in tissue regeneration and in therapeutic and physiological reparation of cartilage, whereby a polynucleotide or oligonucleotide chosen from the nucleotide sequence shown in SEQ ID No. 1 is used as a marker under hybridisation conditions wherein said polynucleotide or oligonucleotide fails to hybridise to a DNA or RNA encoding an integrin subunit α1. Embodiments of this aspect comprise a process, whereby said polynucleotide or oligonucleotide is a polynucleotide or oligonucleotide coding for a peptide chosen from the group comprising peptides of the cytoplasmic domain, the I-domain and the spliced domain, such as a polynucleotide or oligonucleotide coding for a peptide comprising the amino acid sequence KLGFFAHKKIPEEEKREEKLEQ, or comprising the amino acid sequence from about amino acid No. 952 to about amino acid no. 986 of SEQ ID No. 1, or the amino acid sequence from about amino acid No. 140 to about amino acid No. 337 of SEQ ID No. 1. Said pathological conditions may be any pathological conditions involving the integrin subunit α10, such as rheumatoid arthritis, osteoarthrosis or cancer, or atherosclerosis or inflammation. Said cells may be chosen from the group comprising chondrocytes, smooth muscle cells, endothelial cells, osteoblasts and fibroblasts.

In a further aspect the invention relates to a pharmaceutical composition comprising as an active ingredient a pharmaceutical agent or an antibody which is capable of using an integrin heterodimer comprising a subunit α10 and a subunit β, or the subunit α10 thereof, or a homologue or fragment of said integrin or subunit α10 having similar biological activity, as a target molecule. An embodiment of said pharmaceutical composition is intended for use in stimulating, inhibiting or blocking the formation of cartilage, bone or blood vessels. A further embodiment comprises a pharmaceutical composition for use in preventing adhesion between tendon/ligaments and the surrounding tissue after infection, inflammation and after surgical intervention where adhesion impairs the function of the tissue.

The invention is also related to a vaccine comprising as an active ingredient an integrin heterodimer comprising a subunit α10 and a subunit β, or the subunit α10 thereof, or a homologue or fragment of said integrin or subunit α10, or DNA or RNA coding for said integrin subunit α10.

A further aspect of the invention is related to the use of the integrin subunit α10 as defined above as a marker or target in transplantation of cartilage or chondrocytes.

A still further aspect of the invention is related to a method of using binding entities having the capability of binding specifically to an integrin subunit α10 comprising the amino acid sequence shown in SEQ ID No. 1 or SEQ ID No. 2, or an integrin heterodimer comprising said subunit α10 and a subunit β, or to homologues or fragments thereof having similar biological activity, for promoting adhesion of chondrocytes and/or osteoblasts to surfaces of implants to stimulate osseointegration.

The invention is also related to the use of an integrin subunit α10 or an integrin heterodimer comprising said subunit α10 and a subunit β as a target for anti-

adhesive drugs or molecules in tendon, ligament, skeletal muscle or other tissues where adhesion impairs the function of the tissue.

The invention also relates to a method of stimulating, inhibiting or blocking the formation of cartilage or bone, comprising administration to a subject a suitable amount of a pharmaceutical agent or an antibody which is capable of using an integrin heterodimer comprising a subunit α10 and a subunit β, or the subunit α10 thereof, or a homologue or fragment of said integrin or subunit α10 having similar biological activity, as a target molecule.

In another embodiment the invention is related to a method of preventing adhesion between tendon/ligaments and the surrounding tissue after infection, inflammation and after surgical intervention where adhesion impairs the function of the tissue, comprising administration to a subject a suitable amount of a pharmaceutical agent or an antibody which is capable of using a integrin heterodimer comprising a subunit α10 and a subunit β, or the subunit α10 thereof, or a homologue or fragment of said integrin or subunit α10 having similar biological activity, as a target molecule.

The invention also relates to a method of stimulating extracellular matrix synthesis and repair by activation or blockage of an integrin heterodimer comprising a subunit α10 and a subunit β, or of the subunit α10 thereof, or of a homologue or fragment of said integrin or subunit α10 having similar biological activity.

In a further aspect the invention relates to a method of in vitro detecting the presence of integrin binding entities, comprising interaction of an integrin heterodimer comprising a subunit α10 and a subunit β, or the subunit α10 thereof, or a homologue or fragment of said integrin or subunit, with a sample, thereby causing said integrin, subunit α10, or homologue or fragment thereof having similar biological activity, to modulate

the binding to its natural ligand or other integrin binding proteins present in said sample.

The invention also relates to a method of in vitro studying consequences of the interaction of a human heterodimer integrin comprising a subunit $\alpha 10$ and a subunit β, or the subunit $\alpha 10$ thereof, or a homologue or fragment of said integrin or subunit, with an integrin binding entity and thereby initiate a cellular reaction. Said consequences may be measured as alterations in cellular functions.

A still further aspect of the inventions relates to a method of using DNA or RNA encoding an integrin subunit $\alpha 10$ or homologues or fragments thereof as a molecular target. In an embodiment of this aspect, a polynucleotide or oligonucleotide hybridises to the DNA or RNA encoding an integrin subunit $\alpha 10$ or homologues or fragments thereof, whereby said polynucleotide or oligonucleotide fails to hybridise to a DNA or RNA encoding en integrin subunit $\alpha 1$.

The invention also relates to a method of using a human heterodimer integrin comprising a subunit $\alpha 10$ and a subunit β, or the subunit $\alpha 10$ thereof, or a homologue or fragment of said integrin or subunit, or a DNA or RNA encoding an integrin subunit $\alpha 10$ or homologues or fragments thereof, as a marker or target molecule during angiogenesis.

BRIEF DESCRIPTION OF THE FIGURES

Fig.1 Affinity purification of the $\alpha 10$ integrin subunit on collagen type II-Sepharose.

Fig. 2. Amino acid sequences of peptides from the bovine $\alpha 10$ integrin subunit.

Fig. 3a. Affinitypurification and immunoprecipitation of the integrin subunit $\alpha 10$ from bovine chondrocytes.

Fig. 3b. Affinitypurification and immunoprecipitation of the integrin subunit $\alpha 10$ from human chondrocytes.

Fig. 3c. Affinitypurification and immunoprecipitation of the integrin subunit α10 from human chondrosarcoma cells.

Fig. 4. A 900 bp PCR-fragment corresponding to the bovine integrin subunit α10

Fig. 5. Schematic map of the three overlapping α10 clones.

Fig. 6. Nucleotide sequence and deduced amino acid sequence of the human α10 integrin subunit.

Fig. 7. Northern blot of integrin α10 mRNA.

Fig. 8 Immunoprecipitation of the α10 integrin subunit from human chondrocytes using antibodies against the cytoplasmic domain of α10 (a). Western blot of the α10 associated β-chain (b).

Fig. 9. Immunostaining of α10 integrin in human articular cartilage.

Fig. 10 Immunostaining of α10 integrin in 3 day mouse limb cartilage.

Fig 11. Immunostaining of α10 integrin in 13.5 day mouse embryo.

Fig 12. Hybridisation of α10 mRNA in various human tissues.

Fig. 13 Immunostaining of fascia around tendon (a), skeletal muscle (b) and heart valves (c) in 3 day mouse limb.

Fig. 14. PCR fragments corresponding to α10 integrin subunit from human chondrocytes, human endothelial cells, human fibroblasts and rat tendon.

Fig 15. Partial genomic nucleotide sequence of the human integrin subunit α10.

Fig 16. Upregulation of α10 integrin subunit in chondrocytes cultured in alginate.

Fig 17. Immunoprecipitation of the α10 integrin subunit from human smooth muscle cells

DETAILED DESCRIPTION OF THE INVENTION

The present invention demonstrate that human and

bovine chondrocytes express a novel, collagen type II-binding integrin in the β1-family. An earlier study presented some evidence for that human chondrosarcoma cells also express this integrin (25). Immunoprecipitation experiments using antibodies against the integrin subunit β1 revealed that this novel α-integrin subunit had an apparent molecular weight (M_r) of approximately 160 kDa under reducing conditions, and was slightly larger than the α2 integrin subunit. To isolate this α-subunit collagen type II-binding proteins were affinity purified from bovine chondrocytes. The chondrocyte lysate was first applied to a fibronectin-Sepharose precolumn and the flow through was then applied to a collagen type II-Sepharose column. A protein with M_r of approximately 160 kD was specifically eluted with EDTA from the collagen column but not from the fibronectin column. The M_r of this protein corresponded with the M_r of the unidentified β1-related integrin subunit. The 160 kD protein band was excised from the SDS-PAGE gel, digested with trypsin and the amino acid sequences of the isolated peptides were analysed.

Primers corresponding to isolated peptides amplified a 900 bp PCR-fragment from bovine cDNA which was cloned, sequenced and used for screening of a human articular chondrocyte λZapII cDNA library to obtain the human integrin α-subunit homologue. Two overlapping clones, hc1 and hc2 were isolated, subcloned and sequenced. These clones contained 2/3 of the nucleotide sequence including the 3' end of the cDNA. A third clone which contained the 5'end of the α10 cDNA, was obtained using the RACE technique. Sequence analysis of the 160 kD protein sequence showed that it was a member of the integrin α-subunit family and the protein was named α10.

The deduced amino acid sequence of α10 was found to share the general structure of the integrin α-subunits described in previously published reports (6-21). The large extracellular N-terminal part of α10 contains a

seven-fold repeated sequence which was recently predicted to fold into a β-propeller domain (32). The integrin subunit α10 contains three putative divalent cation-binding sites (DxD/NxD/NxxxD) (53), a single spanning transmembrane domain and a short cytoplasmic domain. In contrast to most α-integrin subunits the cytoplasmic domain of α10 does not contain the conserved sequence KxGFF (R/K) R. The predicted amino acid sequence in α10 is KLGFFAH. Several reports indicate that the integrin cytoplasmic domains are crucial in signal transduction (54) and that membrane-proximal regions of both α- and β-integrin cytoplasmic domains are involved in modulating conformation and affinity state of integrins (55-57). It is suggested that the GFFKR motif in α-chains are important for association of integrin subunits and for transport of the integrin to the plasma membrane (58). The KxGFFKR domain has been shown to interact with the intracellular protein calreticulin (59) and interestingly, calreticulin-null embryonic stem cells are deficient in integrin-mediated cell adhesion (60). It is therefor possible that the sequence KLGFFAH in α10 have a key function in regulating the affinity between α10β1 and matrix proteins.

Integrin α subunits are known to share an overall identity of 20-40% (61). Sequence analysis showed that the α10 subunit is most closely related to the I-domain containing α-subunits with the highest identity to α1 (37%) and α2 (35%). The integrins α1β1 and α2β1 are known receptors for both collagens and laminins (24;62;63) and we have also recently demonstrated that α2β1 interacts with the cartilage matrix protein chondroadherin (42). Since α10β1 was isolated on a collagen type II-Sepharose, we know that collagen type II is a ligand for α10β1. We have also shown by affinity purification experiments that α10β1 interacts with collagen type I but it remains to be seen whether laminin or chondroadherin are also ligands for this integrin.

The α10 associated β-chain migrated as the β1 integrin subunit both under reducing and non-reducing conditions. To verify that the α10 associated β-chain indeed is β1, chondrocyte lysates were immunoprecipitated with antibodies against α10 or β1 followed by Western blot using antibodies against the β1-subunit. These results clearly demonstrated that α10 is a member of the β1-integrin family. However, the possibility that α10 combine also with other β-chains can not be excluded..

A polyclonal peptide antibody raised against the cytoplasmic domain of α10 precipitated two protein bands with M_r of approximately 160 kD (α10) and 125 kD (β1) under reducing conditions. Immunohistochemistry using the α10-antibody showed staining of the chondrocytes in tissue sections of human articular cartilage. The antibody staining was clearly specific since preincubation of the antibody with the α10-peptide completely abolished the staining. Immunohistochemical staining of mouse limb sections from embryonic tissue demonstrated that α10 is upregulated during condensation of the mesenchyme. This indicate that the integrin subunit α10 is important during the formation of cartilage. In 3 day old mice α10 was found to be the dominating collagen binding integrin subunit which point to that α10 has a key function in maintaining normal cartilage functions.

Expression studies on the protein and mRNA level show that the distribution of α10 is rather restrictive. Immunohistochemistry analyses have shown that α10 integrin subunit is mainly expressed in cartilage but it is also found in perichondrium, periosteum, ossification groove of Ranvier, in fascia surrounding tendon and skeletal muscle and in the tendon-like structures in the heart valves. This distribution point to that α10 integrin subunit is present also on fibroblasts and osteoblasts. PCR amplification of cDNA from different cell types revealed the presence of an alternatively spliced α10 integrin subunit. This spliced α10 was domi-

nating in fibroblasts which suggests that α10 in fibroblasts may have a different function compared to α10 present on chondrocytes.

Expression of the integrin subunit α10 was found to decrease when chondrocytes were cultured in monolayer. In contrast, the expression of α10 was found to increase when the cells were cultured in alginate beads. Since the latter culturing model is known to preserve the phenotype of chondrocytes the results suggest that α10 can function as marker for a differentiated chondrocyte.

Adhesion between tendon/ligaments and the surrounding tissue is a well-known problem after infection, injury and after surgical intervention. Adhesion between tendon and tendon sheets impairs the gliding function and cause considerable problems especially during healing of tendons in e.g. the hand and fingers leading to functional incapacity. The localisation of the α10 integrin subunit in the fascia of tendon and skeletal muscle makes α10 a possible target for drugs and molecules with anti-adhesive properties that could prevent impairment of the function of tendon/ligament. The integrin subunit α10 can also be a target for drugs or molecules with anti-adhesive properties in other tissues where adhesion is a problem.

EXAMPLES

Example 1

Affinity purification of the α10integrin subunit on collagen type II-Sepharose.

Materials and Methods

Bovine chondrocytes, human chondrocytes or human chondrosarcoma cells were isolated as described earlier [Holmvall et al, Exp Cell Res, 221, 496-503 (1995), Camper et al, JBC, 273, 20383-20389 (1998)]. A Triton X-100 lysate of bovine chondrocytes was applied to a fibronectin-Sepharose precolumn followed by a collagen

type II-Sepharose column and the integrin subunit α10 was eluted from the collagen type II-column by EDTA (Camper et al, JBC, 273, 20383-20389 (1998). The eluted proteins were precipitated by methanol/chloroform, separated by SDS-PAGE under reducing conditions and stained with Coomassie blue. (Camper et al, JBC, 273, 20383-20389 (1998). Peptides from the α10 protein band were isolated by in-gel digestion with a trypsin and phase liquid chromatography and sequenced by Edman degradation (Camper et al, JBC, 273, 20383-20389 (1998).

Results

Fig 1 shows EDTA-eluted proteins from the fibronectin-Sepharose (A), flow-through from the collagen type II-Sepharose column (B) and EDTA-eluted proteins from the collagen type II-Sepharose (C). The α10 integrin subunit (160 kDa) which was specifically eluted from the collagen type II column is indicated with an arrow. Figure 2 shows the amino acid sequences of six peptides that were isolated from the bovine integrin subunit α10. Figures 3 a, b, and c show that the α10 integrin subunit is present on bovine chondrocytes (3a), human chondrocytes (3b) and human chondrosarcoma cells (3c). The affinity for collagen type II, the coprecipitation with β1-integrin subunit and the molecular weight of 160 kDa under reducing conditions identify the α10 integrin subunit on the different cells. These results show that α10 can be isolated from chondrocytes and from chondrosarcoma cells.

Example 2

Amplification of PCR fragment corresponding to bovine α10 integrin subunit.

Materials and methods

The degenerate primers GAY AAY ACI GCI CAR AC (DNTAQT, forward) and TIA TIS WRT GRT GIG GYT (EPHHSI, reverse) were used in PCR (Camper et al, JBC, 273, 20383-20389 (1998) to amplify the nucleotide sequence corresponding to the bovine peptide 1 (Figure 2). A 900 bp

PCR-fragment was then amplified from bovine cDNA using an internal specific primer TCA GCC TAC ATT CAG TAT (SAYIQY, forward) corresponding to the cloned nucleotide sequence of peptide 1 together with the degenerate primer ICK RTC CCA RTG ICC IGG (PGHWDR, reverse) corresponding to the bovine peptide 2 (Figure2). Mixed bases were used in positions that were twofold degenerate and inosines were used in positions that are three- or fourfold degenerate. mRNA isolation and cDNA synthesis was done as earlier described (Camper et al, JBC, 273, 20383-20389 (1998)). The purified fragment was cloned, purified and sequenced as earlier described (Camper et al, JBC, 273, 20383-20389 (1998)).

Results

The nucleotide sequence of peptide 1 (Figure 2) was obtained by PCR-amplification, cloning and sequencing of bovine cDNA. From this nucleotide sequence an exact primer was designed and applied in PCR-amplification with degenerate primers corresponding to peptides 2-6 (Figure 2). Primers corresponding to peptides 1 and 2 amplified a 900 bp PCR-fragment from bovine cDNA (Figure 4).

Example 3

Cloning and sequence analysis of the human α10 integrin subunit

Material and methods

The cloned 900bp PCR-fragment, corresponding to bovine α10-integrin, was digoxigenin-labelled according to the DIG DNA labelling kit (Boehringer Mannheim) and used as a probe for screening of a human articular chondrocyte λZapII cDNA library (provided by Michael Bayliss, The Royal Veterinary Basic Sciences, London, UK)(52). Positive clones containing the pBluescript SK+ plasmid with the cDNA insert were rescued from the ZAP vector by *in vivo* excision as described in the ZAP-cDNA® synthesis kit (Stratagene). Selected plasmids were purified and

sequenced as described earlier (Camper et al, JBC, 273, 20383-20389 (1998)) using T3, T7 and internal specific primers. To obtain cDNA that encoded the 5' end of α10 we designed the primer AAC TCG TCT TCC AGT GCC ATT CGT GGG (reverse; residue 1254-1280 in α10 cDNA) and used it for rapid amplification of the cDNA 5' end (RACE) as described in the Marathon™ cDNA Amplification kit (Clontech INC., Palo Alto, CA).

Results

Two overlapping clones, hc1 and hc2 (Figure 5), were isolated, subcloned and sequenced. These clones contained 2/3 of the nucleotide sequence including the 3' end of the cDNA. A third clone (race1; Figure 5), which contained the 5'end of the α10 cDNA, was obtained using the RACE technique. From these three overlapping clones of α10 cDNA, 3884 nucleotides were sequenced The nucleotide sequence and deduced amino acid sequence is shown in Figure 6. The sequence contains a 3504-nucleotide open reading frame that is predicted to encode a 1167 amino acid mature protein. The signal peptide cleavage site is marked with an arrow, human homologues to bovine peptide sequences are underlined and the I-domain is boxed. Metal ion binding sites are indicated with a broken underline, potential N-glycosylation sites are indicated by an asterisk and the putative transmembrane domain is double underlined. The normally conserved cytoplasmic sequence is indicated by a dot and dashed broken underline.

Sequence analysis demonstrate that α10 is a member of the integrin α-subunit family.

Example 4

Identification of a clone containing a splice variant of α10

One clone which was isolated from the human chondrocyte library (see Example 3) contained a sequence that was identical to the sequence of α10 integrin subunit except that the nucleotides between nt positions

2942 and 3055 were deleted. The splice variant of α10 was verified in PCR experiment using primers flanking the splice region (see figure 14).

Example 5

Identification of α10 integrin subunit by Northern blot

Material and methods

Bovine chondrocyte mRNA was purified using a QuickPrep®Micro mRNA Purification Kit (Pharmacia Biotech, Uppsala, Sweden), separated on a 1% agarose-formaldehyde gel, transferred to nylon membranes and immobilised by UV crosslinking. cDNA-probes were 32P-labelled with Random Primed DNA Labeling Kit (Boehringer Mannheim). Filters were prehybridised for 2-4 hours at 42°C in 5x SSE, 5x Denharts solution, 0.1 % SDS, 50 µg/ml salmon sperm DNA and 50% formamide and then hybridised over night at 42 °C with the same solution containing the specific probe (0.5-1 x 106 cpm/ml). Specifically bound cDNA-probes were analysed using the phosphoimager system (Fuji). Filters were stripped by washing in 0.1% SDS, for 1 hour at 80°C prior to re-probing. The α10-integrin cDNA-probe was isolated from the race1-containing plasmid using the restriction enzymes BamHI (GIBCO BRL) and NcoI (Boehringer Mannheim). The rat β1-integrin cDNA probe was a kind gift from Staffan Johansson, Uppsala, Sweden.

Results

Northern blot analysis of mRNA from bovine chondrocytes showed that a human α10 cDNA-probe hybridised with a single mRNA of approximately 5.4 kb (Figure 7). As a comparison, a cDNA-probe corresponding to the integrin subunit α1 was used. This cDNA-probe hybridised a mRNA-band of approximately 3.5 kb on the same filter. These results show that a cDNA-probe against α10 can be used to identify the α10 integrin subunit on the mRNA level.

Example 6

Preparation of antibodies against the integrin subunit α10

A peptide corresponding to part of the α10 cytoplasmic domain, Ckkipeeekreekle (see figure 6) was synthesised and conjugated to keyhole limpet hemocyanin (KLH). Rabbits were immunised with the peptide-KLH conjugate to generate antiserum against the integrin subunit α10. Antibodies recognising α10 were affinity purified on an peptide-coupled column (Innovagen AB).

Example 7

Immunoprecipitation of the integrin subunit α10 from chondrocytes

Material and methods

Human chondrocytes were ^{125}I-labelled, lyzed with Triton X-100 and immunoprecipitated as earlier described (Holmvall et al, Exp Cell Res, 221, 496-503 (1995), Camper et al, JBC, 273, 20383-20389 (1998)). Triton X-100 lysates of 125I-labeled human chondrocytes were immunoprecipitated with polyclonal antibodies against the integrin subunits β1, α1, α2, α3 or α10. The immunoprecipitated proteins were separated by SDS-PAGE (4-12%) under non-reducing conditions and visualised using a phosphoimager. Triton X-100 lysates of human chondrocytes immunoprecipitated with α10 or β1 were separated by SDS-PAGE (8%) under non-reducing conditions and analysed by Western blot using the polyclonal β1 antibody and chemiluminescent detection as described in Camper et al, JBC, 273, 20383-20389 (1998).

Results

The polyclonal peptide antibody, raised against the cytoplasmic domain of α10, precipitated two protein bands with Mr of approximately 160 kD (α10) and 125 kD (β1) under reducing conditions. The α10 associated β-chain migrated as the β1 integrin subunit (Figure 8a). To verify that the α10 associated β-chain in chondrocytes

indeed is β1, chondrocyte lysates were immunoprecipitated with antibodies against α10 orb β1 followed by Western blot using antibodies against the β1-subunit (Figure 8b). These results clearly demonstrated that α10 is a member of the β1-integrin family. However, the results do not exclude the possibility that α10 can associate with other β-chains in other situations.

Example 8

Immunohistochemical staining of the integrin subunit α10 in human and mouse cartilage

Material and methods

Frozen sections of adult cartilage (trochlear groove) obtained during surgery (provided by Anders Lindahl, Salgrenska Hospital, Gothenburg, Sweden and frozen sections from of 3 day old mouse limb were fixed and prepared for immunohistochemistry as earlier described (Camper et al, JBC, 273, 20383-20389 (1998)). Expression of α10 integrin subunit was analysed using the polyclonal antibody against the cytoplasmic domain as a primary antibody (see Example 6) and a secondary antibody conjugated to peroxidase.

Results

Figures 9 show immunostaining of human adult articular cartilage.

The α10-antibody recognising the cytoplasmic domain of α10 stained the chondrocytes in tissue sections of human articular cartilage (A). The staining was depleted when the antibody was preincubated with the α10- peptide (B). A control antibody recognising the α9 integrin subunit did not bind to the chondrocyte (C).

Figures 10 shows that the α10 antibody stain the majority of chondrocytes in the growing bone anlage (a and b). The α10 antibody also recognised cells in the ossification groove of Ranvier (b), especially the osteoblast in the bone bark which are lining the cartilage in the metaphys are highly positive for α10. The

cells in the ossification groove of Ranvier are believed to be important for the growth in diameter of the bone. The integrin subunit α10 is also highly expressed in perichondrium and periosteum. Cell in these tissues are likely important in the repair of the cartilage tissue. The described localisation of the integrin subunit α10 suggest that this integrin is important for the function of the cartilage tissue.

Example 9

Immunohistochemical staining of the integrin subunit α10 during mouse development

Material and methods

Frozen sections from mouse embryos (13.5 days) were investigated for expression of α10 by immunhistochemistry as described in Camper et al, JBC, 273, 20383-20389 (1998). Expression of α10 integrin subunit was analysed using the polyclonal antibody against the cytoplasmic domain as a primary antibody (see Example 6) and a secondary antibody conjugated to peroxidase. The embryo sections were also investigated for expression of integrin subunit α1 (monoclonal antibody from Pharmingen) and collagen type II (monoclonal antibody, kind gift from Dr John Mo, Lund University, Sweden).

Results

Figure 11 show that α10 integrin subunit is unregulated in the limb when the mesenchymal cells undergo condensation to form cartilage (a). Especially the edge of the newly formed cartilage has high expression of α10. The formation of cartilage is verified by the high expression of the cartilage specific collage type II (b). The control antibody against α1 integrin subunit showed only weak expression on the cartilage (c). In other experiments expression of α10 was found in all cartilage containing tissues in the 3 day old mouse including limbs, ribs and vertebrae. The upregulation of α10 during formation of cartilage suggest that this integrin subunit is

important both in the development of cartilage and bone and in the repair of damaged cartilage tissue.

Example 10

mRNA expression of α10 in tissues other than articular cartilage

Material and methods

Expression of α10 integrin subunit was examined on the mRNA level in different human tissues. A Northern dot blot with immobilised mRNA from the listed tissues in Figure 12 was hybridised with an α10 integrin cDNA probe isolated from the race 1-containing plasmid using the restriction enzymes *Bam*H1 and *Nco*1. The degree of hybridisation was analysed using a phospho imager. The following symbols denote mRNA level in increasing order: −, +, ++, +++, ++++.

Results

Analysis of the hybridised mRNA showed that α10 was expressed in aorta, trachea, spinal cord, heart, lung, and kidney (Figure 12). All other tissues appeared negative for α10 expression. These results point to a restricted distribution of the α10 integrin subunit.

Example 11

Immunohistochemical staining of α10 in fascia around tendon and skeletal muscle and in tendon structures in heart valves.

Materials and methods

Frozen sections of adult cartilage (trochlear groove) obtained during surgery (provided by Anders Lindahl, Salgrenska Hospital, Gothenburg, Sweden and frozen sections from of 3 day old mouse limb were fixed and prepared for immunohistochemistry as earlier described (Camper et al, JBC, 273, 20383-20389 (1998)). Expression of α10 integrin subunit was analysed using the polyclonal antibody against the cytoplasmic domain as a pri-

mary antibody (see Example 6) and a secondary antibody conjugated to peroxidase.

Results

As shown in figures 13 expression of α10 was found in the fascia surrounding tendon (a) and skeletal muscle (b) and in the tendon structures in the heart valves (c). This localisation suggest that α10 can bind to other matrix molecules in addition to the cartilage specific collagen type II. The localisation of the integrin α10 on the surface of tendons indicate that α10 can be involved in unwanted adhesion that often occurs between tendon/ ligaments and the surrounding tissue after infection, injury or after surgery.

Example 12

mRNA expression of α10 integrin subuhit in chondrocytes, endothelial cells and fibroblasts.

Material and methods

Isolation of mRNA, synthesis of cDNA and PCR amplification was done as earlier described (Camper et al, JBC, 273, 20383-20389 (1998)).

Results

Figure 14 shows PCR amplification of α10 cDNA from human articular chondrocytes (lanes A6 and B1), human umbilical vein endothelial cells (lane A2), human fibroblasts (lane A4) and rat tendon (Fig 14b, lane B2). Lanes 1, 3, and 5 in figure 14 A show amplified fragments corresponding to the integrin subunit α2 in endothelial cells, fibroblasts and chondrocytes, respectively. cDNA-primers corresponding to the α10 sequence positions nt 2919-2943 (forward) and nt 3554-3578 (reverse) (see Figure 6) were used to amplify α10 cDNA from the different cells. The figure shows that α10 was amplified in all three cell types. Two fragments of α10 was amplified which represent the intact form of α10 (larger fragment) and a splice variant (smaller fragment). The larger frag-

ment was dominating in chondrocytes while the smaller fragment was more pronounced in tendon (B2).

Example 13

Construction of α10 mammalian expression vector.

The full length protein coding sequence of α10 (combined from 3 clones, see figure 6) was inserted into the mammalian expression vector, pcDNA3.1/Zeo (Invitrogen). The vector contains SV40 promoter and Zeosin selection sequence. The α10 containing expression vector was transfected into cells that express the β1-integrin subunit but lack expression of the α10 subunit. Expression of the α10 integrin subunit on the cell surface can be analysed by immunoprecipitation and/or flow cytometry using antibodies specific for α10. The ligand binding capacity and the function of the inserted α10 integrin subunit can be demonstrated in cell adhesion experiment and in signalling experiments.

Example 14

Construction of mammalian expression vector containing a splice variant of α10.

The full length protein coding sequence of the splice variant of α10 (nt 2942-nt3055 deleted) was inserted into the mammalian expression vector pcDNA3 (see Example 13). Expression and function of the splice variant can be analysed as described in example 13 and compared with the intact α10 integrin subunit.

Example 15

Partial isolation and characterisation of the α10 integrin genomic DNA

Material and methods

Human α10 cDNA, isolated from the racel-containing plasmid using the restriction enzymes *Bam*HI (GIBCO BRL) and *Nco*I (Boehringer Mannheim), was ^{32}P-labelled and used as a probe for screening of a mouse 129 cosmid library

(provided by Reinhard Fässler, Lund University). Positive clones were isolated and subcloned. Selected plasmids were purified and sequenced as described earlier (Camper et al, JBC, 273, 20383-20389 (1998)) using T3, T7 and internal specific primers. Primers corresponding to mouse genomic DNA were then constructed and used in PCR to amplify and identify the genomic sequence of α10 from the cosmid clones.

Results

Figure 15 shows 7958 nt of the α10 gene. This partial genomic DNA sequence of α10 integrin contains 8 exons, and a Kozak sequence. The mouse genomic α10 sequence was used to generate a targeting vector for knockout experiments.

Example 16

Upregulation of α10 integrin subunit in chondrocytes cultured in alginate beads

Material and methods

Human chondrocytes cultured in monolayer for 2 weeks were detached with trypsin-EDTA and introduced into alginate beads. Chondrocytes cultured in alginate are known to preserve their phenotype while chondrocytes cultured in monolayer are dedifferentiated. After 11 days chondrocytes cultured either in alginate or on monolayer were isolated and surface labelled with ^{125}I. The α10 integrin subunit was then immunoprecipitated with polyclonal antibodies recognising the cytoplasmic domain of α10 (see Example 6 and Camper et al, JBC, 273, 20383-20389 (1998)).

Results

As shown in figure 16 chondrocytes cultured in alginate beads (lanes 3 and 4) upregulated their protein expression of α10β1. This was in contrast to chondrocytes cultured in monolayer (lanes 1 and 2) which had a very low expression of α10β1. Immunoprecipitation with ab control antibody is shown in lanes 1 and 3.It is known that

chondrocytes preserve their cartilage specific matrixproduction in alginate cultures but not in monolayer culture which point to that alginate preserve the phenotype of chondrocytes. These results support that α10 integrin subunit can be used as a marker for differentiated chondrocytes.

Example 17

Immunoprecipitation of the α10 integrin subunit from human smooth muscle cells.

Material and methods

Human smooth muscle cells were isolated from human aorta. After one week in culture the cells were ^{125}I-labelled, lysed and immunoprecipitated with antibodies against the integrin subunit β1 (lane 1), α1 (lane 2), α2 (lane 3), α10 (lane 4), α3 (lane 5), control (lane 6) (Figure 17). The experiment was done as described in Example 7.

Results

The α10 antibody precipitated two bands from the smooth muscle cells corresponding to the α10 and the β1 integrin subunit (Fig. 17).

Example 18

Construction of bacterial expression vector containing sequence for α10 splice region.

A plasmid for intracellular expression in E. coli of the alternatively spliced region (amino acid pos. 952-986, SEQ. ID 1) was constructed as described. The alternatively spliced region were back-translated using the E. coli high frequency codon table, creating a cDNA sequence of 96% identity with the original sequence (SEQ. ID 1 nucleotide pos 2940-3044). Using sequence overlap extension (Horton et al., Biotechniques 8:528, 1990) primer α10pfor (tab. I) and α10prev (tab. I) was used to generate a double stranded fragment encoding the α10 amino acid sequence. This fragment was used as a PCR

template with primers α10pfor2 (tab. I) and α10prev2 (tab. I) in order to generate restriction enzyme site for sub-cloning in a pET vector containing the Z-domain of staphylococcal protein A, creating a fusion of the α10 spliced region with the amino terminal of the Z-domain with trombin cleavage site residing in-between. The fragment generated in the second PCR reaction is shown (SEQ ID No. 3) also indicating the unique restriction enzymes used for sub-cloning in the expression vector.

Table I

α10pfor	5′-GTTCAGAACCTGGGTTGCTACGTTGTTTCCGGTCTGATCATCTCCGCTCTGCTGCCGGCTGT-3′
α10pfor2	5′-GGGGCATATGGTTCAGAACCTGGGTTGCTACGTTG-3′
α10prev	5′-GATAACCTGGGACAAGCTTAGGAAGTAGTTACCACCGTGAGCAACAGCCGGCAGCAGAGCGGA-3′
α10prev2	5′-GGGGGGATCCGCGCGGCACCAGGCCGCTGATAACCTGGGACAAGCTTAGGAAGT-3′

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SEQUENCE LISTING

(1) GENERAL INFORMATION:
  (i) NUMBER OF SEQUENCES: 2

(2) INFORMATION FOR SEQ ID NO. 1:
  (i) SEQUENCE CHARACTERISTICS:
    (A) LENGTH: 3884 base pairs
    (B) TYPE: nucleic acid and amino acid
    (C) STRANDEDNESS: double
    (D) TOPOLOGY: linear

  (ii) MOLECULAR TYPE: cDNA
  (vi) ORIGINAL SOURCE:
    (E) ORGANISM: human
    (F) CELLTYPE: chondrocyte
  (xi) SEQUENCE DESCRIPTION: SEQ ID NO. 1:

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a                              M  E  L  P  F  V  T  H  L  F  L  P  L   -

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     61  ---------+---------+---------+---------+---------+---------+ 120
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a        V  F  L  T  G  L  C  S  P  F  N  L  D  E  H  H  P  R  L  F   -

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    121  ---------+---------+---------+---------+---------+---------+ 180
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a        P  G  P  P  E  A  E  F  G  Y  S  V  L  Q  H  V  G  G  G  Q   -

         CGATGGATGCTGGTGGGCGCCCCCTGGGATGGGCCTTCAGGCGACCGGAGGGGGGACGTT
    181  ---------+---------+---------+---------+---------+---------+ 240
         GCTACCTACGACCACCCGCGGGGGACCCTACCCGGAAGTCCGCTGGCCTCCCCCCTGCAA

a        R  W  M  L  V  G  A  P  W  D  G  P  S  G  D  R  R  G  D  V   -

         TATCGCTGCCCTGTAGGGGGGGCCCACAATGCCCCATGTGCCAAGGGCCACTTAGGTGAC
    241  ---------+---------+---------+---------+---------+---------+ 300
         ATAGCGACGGGACATCCCCCCCGGGTGTTACGGGGTACACGGTTCCCGGTGAATCCACTG

a        Y  R  C  P  V  G  G  A  H  N  A  P  C  A  K  G  H  L  G  D   -

         TACCAACTGGGAAATTCATCTCATCCTGCTGTGAATATGCACCTGGGGATGTCTCTGTTA
    301  ---------+---------+---------+---------+---------+---------+ 360
         ATGGTTGACCCTTTAAGTAGAGTAGGACGACACTTATACGTGGACCCCTACAGAGACAAT

a        Y  Q  L  G  N  S  S  H  P  A  V  N  M  H  L  G  M  S  L  L   -

         GAGACAGATGGTGATGGGGGATTCATGGCCTGTGCCCCTCTCTGGTCTCGTGCTTGTGGC
    361  ---------+---------+---------+---------+---------+---------+ 420
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a        E  T  D  G  D  G  G  F  M  A  C  A  P  L  W  S  R  A  C  G   -
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      421 ---------+---------+---------+---------+---------+---------+ 480
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a          S  S  V  F  S  S  G  I  C  A  R  V  D  A  S  F  Q  P  Q  G  -

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      481 ---------+---------+---------+---------+---------+---------+ 540
          TCGGACCGTGGGTGACGGGTTGCGACGGGTTGTATGTACCTACAACAGTAACAGAACCTA

a          S  L  A  P  T  A  Q  R  C  P  T  Y  M  D  V  V  I  V  L  D  -

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a          G  S  N  S  I  Y  P  W  S  E  V  Q  T  F  L  R  R  L  V  G  -

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      601 ---------+---------+---------+---------+---------+---------+ 660
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a          K  L  F  I  D  P  E  Q  I  Q  V  G  L  V  Q  Y  G  E  S  P  -

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      661 ---------+---------+---------+---------+---------+---------+ 720
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a          V  H  E  W  S  L  G  D  F  R  T  K  E  E  V  V  R  A  A  K  -

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a          N  L  S  R  R  E  G  R  E  T  K  T  A  Q  A  I  M  V  A  C  -

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      781 ---------+---------+---------+---------+---------+---------+ 840
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a          T  E  G  F  S  Q  S  H  G  G  R  P  E  A  A  R  L  L  V  V  -

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a          V  T  D  G  E  S  H  D  G  E  E  L  P  A  A  L  K  A  C  E  -

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      901 ---------+---------+---------+---------+---------+---------+ 960
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a          A  G  R  V  T  R  Y  G  I  A  V  L  G  H  Y  L  R  R  Q  R  -

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      961 ---------+---------+---------+---------+---------+---------+ 1020
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a          D  P  S  S  F  L  R  E  I  R  T  I  A  S  D  P  D  E  R  F  -

          TTCTTCAATGTCACAGATGAGGCTGCTCTGACTGACATTGTGGATGCACTAGGAGATCGG
     1021 ---------+---------+---------+---------+---------+---------+ 1080
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a          F  F  N  V  T  D  E  A  A  L  T  D  I  V  D  A  L  G  D  R  -
```

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     ATTTTTGGCCTTGAAGGGTCCCATGCAGAAAACGAAAGCTCCTTTGGGCTGGAAATGTCT
1081 ---------+---------+---------+---------+---------+---------+ 1140
     TAAAAACCGGAACTTCCCAGGGTACGTCTTTTGCTTTCGAGGAAACCCGACCTTTACAGA

a     I  F  G  L  E  G  S  H  A  E  N  E  S  S  F  G  L  E  M  S   -

     CAGATTGGTTTCTCCACTCATCGGCTAAAGGATGGGATTCTTTTTGGGATGGTGGGGGCC
1141 ---------+---------+---------+---------+---------+---------+ 1200
     GTCTAACCAAAGAGGTGAGTAGCCGATTTCCTACCCTAAGAAAAACCCTACCACCCCCGG

a     Q  I  G  F  S  T  H  R  L  K  D  G  I  L  F  G  M  V  G  A   -

     TATGACTGGGGAGGCTCTGTGCTATGGCTTGAAGGAGGCCACCGCCTTTTCCCCCCACGA
1201 ---------+---------+---------+---------+---------+---------+ 1260
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a     M  A  L  E  D  E  F  P  P  A  L  Q  N  H  A  A  Y  L  G  Y   -

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1321 ---------+---------+---------+---------+---------+---------+ 1380
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a     S  V  S  S  M  L  L  R  G  G  R  R  L  F  L  S  G  A  P  R   -

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1381 ---------+---------+---------+---------+---------+---------+ 1440
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a     F  R  H  R  G  K  V  I  A  F  Q  L  K  K  D  G  A  V  R  V   -

     GCCCAGAGCCTCCAGGGGGAGCAGATTGGTTCATACTTTGGCAGTGAGCTCTGCCCATTG
1441 ---------+---------+---------+---------+---------+---------+ 1500
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a     A  Q  S  L  Q  G  E  Q  I  G  S  Y  F  G  S  E  L  C  P  L   -

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1501 ---------+---------+---------+---------+---------+---------+ 1560
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a     D  T  D  R  D  G  T  T  D  V  L  L  V  A  A  P  M  F  L  G   -

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1561 ---------+---------+---------+---------+---------+---------+ 1620
     GGGGTCTTGTTCCTTTGTCCTGCACAAATACACATAGACCATCCGGTCGTCAGGAACGAC

a     P  Q  N  K  E  T  G  R  V  Y  V  Y  L  V  G  Q  Q  S  L  L   -

     ACCCTCCAAGGAACACTTCAGCCAGAACCCCCCCAGGATGCTCGGTTTGGCTTTGCCATG
1621 ---------+---------+---------+---------+---------+---------+ 1680
     TGGGAGGTTCCTTGTGAAGTCGGTCTTGGGGGGGTCCTACGAGCCAAACCGAAACGGTAC

a     T  L  Q  G  T  L  Q  P  E  P  P  Q  D  A  R  F  G  F  A  M   -

     GGAGCTCTTCCTGATCTGAACCAAGATGGTTTTGCTGATGTGGCTGTGGGGGCGCCTCTG
1681 ---------+---------+---------+---------+---------+---------+ 1740
     CCTCGAGAAGGACTAGACTTGGTTCTACCAAAACGACTACACCGACACCCCCGCGGAGAC

a     G  A  L  P  D  L  N  Q  D  G  F  A  D  V  A  V  G  A  P  L   -
```

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     GAAGATGGGCACCAGGGAGCACTGTACCTGTACCATGGAACCCAGAGTGGAGTCAGGCCC
1741 ---------+---------+---------+---------+---------+---------+ 1800
     CTTCTACCCGTGGTCCCTCGTGACATGGACATGGTACCTTGGGTCTCACCTCAGTCCGGG

a    E  D  G  H  Q  G  A  L  Y  L  Y  H  G  T  Q  S  G  V  R  P  -

     CATCCTGCCCAGAGGATTGCTGCTGCCTCCATGCCACATGCCCTCAGCTACTTTGGCCGA
1801 ---------+---------+---------+---------+---------+---------+ 1860
     GTAGGACGGGTCTCCTAACGACGACGGAGGTACGGTGTACGGGAGTCGATGAAACCGGCT

a    H  P  A  Q  R  I  A  A  A  S  M  P  H  A  L  S  Y  F  G  R  -

     AGTGTGGATGGTCGGCTAGATCTGGATGGAGATGATCTGGTCGATGTGGCTGTGGGTGCC
1861 ---------+---------+---------+---------+---------+---------+ 1920
     TCACACCTACCAGCCGATCTAGACCTACCTCTACTAGACCAGCTACACCGACACCCACGG

a    S  V  D  G  R  L  D  L  D  G  D  D  L  V  D  V  A  V  G  A  -

     CAGGGGGCAGCCATCCTGCTCAGCTCCCGGCCCATTGTCCATCTGACCCCATCACTGGAG
1921 ---------+---------+---------+---------+---------+---------+ 1980
     GTCCCCCGTCGGTAGGACGAGTCGAGGGCCGGGTAACAGGTAGACTGGGGTAGTGACCTC

a    Q  G  A  A  I  L  L  S  S  R  P  I  V  H  L  T  P  S  L  E  -

     GTGACCCCACAGGCCATCAGTGTGGTTCAGAGGGACTGTAGGCGGCGAGGCCAAGAAGCA
1981 ---------+---------+---------+---------+---------+---------+ 2040
     CACTGGGGTGTCCGGTAGTCACACCAAGTCTCCCTGACATCCGCCGCTCCGGTTCTTCGT

a    V  T  P  Q  A  I  S  V  V  Q  R  D  C  R  R  R  G  Q  E  A  -

     GTCTGTCTGACTGCAGCCCTTTGCTTCCAAGTGACCTCCCGTACTCCTGGTCGCTGGGAT
2041 ---------+---------+---------+---------+---------+---------+ 2100
     CAGACAGACTGACGTCGGGAAACGAAGGTTCACTGGAGGGCATGAGGACCAGCGACCCTA

a    V  C  L  T  A  A  L  C  F  Q  V  T  S  R  T  P  G  R  W  D  -

     CACCAATTCTACATGAGGTTCACCGCATCACTGGATGAATGGACTGCTGGGGCACGTGCA
2101 ---------+---------+---------+---------+---------+---------+ 2160
     GTGGTTAAGATGTACTCCAAGTGGCGTAGTGACCTACTTACCTGACGACCCCGTGCACGT

a    H  Q  F  Y  M  R  F  T  A  S  L  D  E  W  T  A  G  A  R  A  -

     GCATTTGATGGCTCTGGCCAGAGGTTGTCCCCTCGGAGGCTCCGGCTCAGTGTGGGGAAT
2161 ---------+---------+---------+---------+---------+---------+ 2220
     CGTAAACTACCGAGACCGGTCTCCAACAGGGGAGCCTCCGAGGCCGAGTCACACCCCTTA

a    A  F  D  G  S  G  Q  R  L  S  P  R  R  L  R  L  S  V  G  N  -

     GTCACTTGTGAGCAGCTACACTTCCATGTGCTGGATACATCAGATTACCTCCGGCCAGTG
2221 ---------+---------+---------+---------+---------+---------+ 2280
     CAGTGAACACTCGTCGATGTGAAGGTACACGACCTATGTAGTCTAATGGAGGCCGGTCAC

a    V  T  C  E  Q  L  H  F  H  V  L  D  T  S  D  Y  L  R  P  V  -

     GCCTTGACTGTGACCTTTGCCTTGGACAATACTACAAAGCCAGGGCCTGTGCTGAATGAG
2281 ---------+---------+---------+---------+---------+---------+ 2340
     CGGAACTGACACTGGAAACGGAACCTGTTATGATGTTTCGGTCCCGGACACGACTTACTC

a    A  L  T  V  T  F  A  L  D  N  T  T  K  P  G  P  V  L  N  E  -

     GGCTCACCCACCTCTATACAAAAGCTGGTCCCCTTCTCAAAGGATTGTGGCCCTGACAAT
2341 ---------+---------+---------+---------+---------+---------+ 2400
     CCGAGTGGGTGGAGATATGTTTTCGACCAGGGGAAGAGTTTCCTAACACCGGGACTGTTA

a    G  S  P  T  S  I  Q  K  L  V  P  F  S  K  D  C  G  P  D  N  -
```

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        GAATGTGTCACAGACCTGGTGCTTCAAGTGAATATGGACATCAGAGGCTCCAGGAAGGCC
   2401 ---------+---------+---------+---------+---------+---------+ 2460
        CTTACACAGTGTCTGGACCACGAAGTTCACTTATACCTGTAGTCTCCGAGGTCCTTCCGG

a       E  C  V  T  D  L  V  L  Q  V  N  M  D  I  R  G  S  R  K  A  -

        CCATTTGTGGTTCGAGGTGGCCGGCGGAAAGTGCTGGTATCTACAACTCTGGAGAACAGA
   2461 ---------+---------+---------+---------+---------+---------+ 2520
        GGTAAACACCAAGCTCCACCGGCCGCCTTTCACGACCATAGATGTTGAGACCTCTTGTCT

a       P  F  V  V  R  G  G  R  R  K  V  L  V  S  T  T  L  E  N  R  -

        AAGGAAAATGCTTACAATACGAGCCTGAGTATCATCTTCTCTAGAAACCTCCACCTGGCC
   2521 ---------+---------+---------+---------+---------+---------+ 2580
        TTCCTTTTACGAATGTTATGCTCGGACTCATAGTAGAAGAGATCTTTGGAGGTGGACCGG

a       K  E  N  A  Y  N  T  S  L  S  I  I  F  S  R  N  L  H  L  A  -

        AGTCTCACTCCTCAGAGAGAGAGCCCAATAAAGGTGGAATGTGCCGCCCCTTCTGCTCAT
   2581 ---------+---------+---------+---------+---------+---------+ 2640
        TCAGAGTGAGGAGTCTCTCTCTCGGGTTATTTCCACCTTACACGGCGGGGAAGACGAGTA

a       S  L  T  P  Q  R  E  S  P  I  K  V  E  C  A  A  P  S  A  H  -

        GCCCGGCTCTGCAGTGTGGGGCATCCTGTCTTCCAGACTGGAGCCAAGGTGACCTTTCTG
   2641 ---------+---------+---------+---------+---------+---------+ 2700
        CGGGCCGAGACGTCACACCCCGTAGGACAGAAGGTCTGACCTCGGTTCCACTGGAAAGAC

a       A  R  L  C  S  V  G  H  P  V  F  Q  T  G  A  K  V  T  F  L  -

        CTAGAGTTTGAGTTTAGCTGCTCCTCTCTCCTGAGCCAGGTCTTTGGGAAGCTGACTGCC
   2701 ---------+---------+---------+---------+---------+---------+ 2760
        GATCTCAAACTCAAATCGACGAGGAGAGAGGACTCGGTCCAGAAACCCTTCGACTGACGG

a       L  E  F  E  F  S  C  S  S  L  L  S  Q  V  F  G  K  L  T  A  -

        AGCAGTGACAGCCTGGAGAGAAATGGCACCCTTCAAGAAAACACAGCCCAGACCTCAGCC
   2761 ---------+---------+---------+---------+---------+---------+ 2820
        TCGTCACTGTCGGACCTCTCTTTACCGTGGGAAGTTCTTTTGTGTCGGGTCTGGAGTCGG

a       S  S  D  S  L  E  R  N  G  T  L  Q  E  N  T  A  Q  T  S  A  -

        TACATCCAATATGAGCCCCACCTCCTGTTCTCTAGTGAGTCTACCCTGCACCGCTATGAG
   2821 ---------+---------+---------+---------+---------+---------+ 2880
        ATGTAGGTTATACTCGGGGTGGAGGACAAGAGATCACTCAGATGGGACGTGGCGATACTC

a       Y  I  Q  Y  E  P  H  L  L  F  S  S  E  S  T  L  H  R  Y  E  -

        GTTCACCCATATGGGACCCTCCCAGTGGGTCCTGGCCCAGAATTCAAAACCACTCTCAGG
   2881 ---------+---------+---------+---------+---------+---------+ 2940
        CAAGTGGGTATACCCTGGGAGGGTCACCCAGGACCGGGTCTTAAGTTTTGGTGAGAGTCC

a       V  H  P  Y  G  T  L  P  V  G  P  G  P  E  F  K  T  T  L  R  -

        GTTCAGAACCTAGGCTGCTATGTGGTCAGTGGCCTCATCATCTCAGCCCTCCTTCCAGCT
   2941 ---------+---------+---------+---------+---------+---------+ 3000
        CAAGTCTTGGATCCGACGATACACCAGTCACCGGAGTAGTAGAGTCGGGAGGAAGGTCGA

a       V  Q  N  L  G  C  Y  V  V  S  G  L  I  I  S  A  L  L  P  A  -

        GTGGCCCATGGGGGCAATTACTTCCTATCACTGTCTCAAGTCATCACTAACAATGCAAGC
   3001 ---------+---------+---------+---------+---------+---------+ 3060
        CACCGGGTACCCCCGTTAATGAAGGATAGTGACAGAGTTCAGTAGTGATTGTTACGTTCG

a       V  A  H  G  G  N  Y  F  L  S  L  S  Q  V  I  T  N  N  A  S  -
```

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       TGCATAGTGCAGAACCTGACTGAACCCCCAGGCCCACCTGTGCATCCAGAGGAGCTTCAA
  3061 ---------+---------+---------+---------+---------+---------+ 3120
       ACGTATCACGTCTTGGACTGACTTGGGGGTCCGGGTGGACACGTAGGTCTCCTCGAAGTT

a      C  I  V  Q  N  L  T  E  P  P  G  P  P  V  H  P  E  E  L  Q  -

       CACACAAACAGACTGAATGGGAGCAATACTCAGTGTCAGGTGGTGAGGTGCCACCTTGGG
  3121 ---------+---------+---------+---------+---------+---------+ 3180
       GTGTGTTTGTCTGACTTACCCTCGTTATGAGTCACAGTCCACCACTCCACGGTGGAACCC

a      H  T  N  R  L  N  G  S  N  T  Q  C  Q  V  V  R  C  H  L  G  -

       CAGCTGGCAAAGGGGACTGAGGTCTCTGTTGGACTATTGAGGCTGGTTCACAATGAATTT
  3181 ---------+---------+---------+---------+---------+---------+ 3240
       GTCGACCGTTTCCCCTGACTCCAGAGACAACCTGATAACTCCGACCAAGTGTTACTTAAA

a      Q  L  A  K  G  T  E  V  S  V  G  L  L  R  L  V  H  N  E  F  -

       TTCCGAAGAGCCAAGTTCAAGTCCCTGACGGTGGTCAGCACCTTTGAGCTGGGAACCGAA
  3241 ---------+---------+---------+---------+---------+---------+ 3300
       AAGGCTTCTCGGTTCAAGTTCAGGGACTGCCACCAGTCGTGGAAACTCGACCCTTGGCTT

a      F  R  R  A  K  F  K  S  L  T  V  V  S  T  F  E  L  G  T  E  -

       GAGGGCAGTGTCCTACAGCTGACTGAAGCCTCCCGTTGGAGTGAGAGCCTCTTGGAGGTG
  3301 ---------+---------+---------+---------+---------+---------+ 3360
       CTCCCGTCACAGGATGTCGACTGACTTCGGAGGGCAACCTCACTCTCGGAGAACCTCCAC

a      E  G  S  V  L  Q  L  T  E  A  S  R  W  S  E  S  L  L  E  V  -

       GTTCAGACCCGGCCTATCCTCATCTCCCTGTGGATCCTCATAGGCAGTGTCCTGGGAGGG
  3361 ---------+---------+---------+---------+---------+---------+ 3420
       CAAGTCTGGGCCGGATAGGAGTAGAGGGACACCTAGGAGTATCCGTCACAGGACCCTCCC

a      V  Q  T  R  P  I  L  I  S  L  W  I  L  I  G  S  V  L  G  G  -

       TTGCTCCTGCTTGCTCTCCTTGTCTTCTGCCTGTGGAAGCTTGGCTTCTTTGCCCATAAG
  3421 ---------+---------+---------+---------+---------+---------+ 3480
       AACGAGGACGAACGAGAGGAACAGAAGACGGACACCTTCGAACCGAAGAAACGGGTATTC

a      L  L  L  L  A  L  L  V  F  C  L  W  K  L  G  F  F  A  H  K  -

       AAAATCCCTGAGGAAGAAAAAAGAGAAGAGAAGTTGGAGCAATGAATGTAGAATAAGGGT
  3481 ---------+---------+---------+---------+---------+---------+ 3540
       TTTTAGGGACTCCTTCTTTTTTCTCTTCTCTTCAACCTCGTTACTTACATCTTATTCCCA

a      K  I  P  E  E  E  K  R  E  E  K  L  E  Q

       CTAGAAAGTCCTCCCTGGCAGCTTTCTTCAAGAGACTTGCATAAAAGCAGAGGTTTGGGG
  3541 ---------+---------+---------+---------+---------+---------+ 3600
       GATCTTTCAGGAGGGACCGTCGAAAGAAGTTCTCTGAACGTATTTTCGTCTCCAAACCCC

       GCTCAGATGGGACAAGAAGCCGCCTCTGGACTATCTCCCCAGACCAGCAGCCTGACTTGA
  3601 ---------+---------+---------+---------+---------+---------+ 3660
       CGAGTCTACCCTGTTCTTCGGCGGAGACCTGATAGAGGGGTCTGGTCGTCGGACTGAACT

       CTTTTGAGTCCTAGGGATGCTGCTGGCTAGAGATGAGGCTTTACCTCAGACAAGAAGAGC
  3661 ---------+---------+---------+---------+---------+---------+ 3720
       GAAAACTCAGGATCCCTACGACGACCGATCTCTACTCCGAAATGGAGTCTGTTCTTCTCG
```

```
     TGGCACCAAAACTAGCCATGCTCCCACCCTCTGCTTCCCTCCTCCTCGTGATCCTGGTTC
3721 ---------+---------+---------+---------+---------+---------+ 3780
     ACCGTGGTTTTGATCGGTACGAGGGTGGGAGACGAAGGGAGGAGGAGCACTAGGACCAAG

     CATAGCCAACACTGGGGCTTTTGTTTGGGGTCCTTTTATCCCCAGGAATCAATAATTTTT
3781 ---------+---------+---------+---------+---------+---------+ 3840
     GTATCGGTTGTGACCCCGAAAACAAACCCCAGGAAAATAGGGGTCCTTAGTTATTAAAAA

     TTGCCTAGGAAAAAAAAAAGCGGCCGCGAATTCGATATCAAGCT
3841 ---------+---------+---------+---------+---- 3884
     AACGGATCCTTTTTTTTTTCGCCGGCGCTTAAGCTATAGTTCGA
```

(2) INFORMATION FOR SEQ ID NO. 2:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 3779 base pairs

(B) TYPE: nucleid acid and amino acid

(C) STRANDEDNESS: double

(D) TOPOLOGY: linear

(E)

(i) MOLECULAR TYPE: cDNA

(vi) ORIGINAL SOURCE:

(A) ORGANISM: human

(B) CELLTYPE: chondrocyte

(xi) SEQUENCE DESCRIPTION: SEQ ID NO. 2:

```
      CAGGTCAGAAACCGATCAGGCATGGAACTCCCCTTCGTCACTCACCTGTTCTTGCCCCTG
    1 ---------+---------+---------+---------+---------+---------+ 60
      GTCCAGTCTTTGGCTAGTCCGTACCTTGAGGGGAAGCAGTGAGTGGACAAGAACGGGGAC

                             M  E  L  P  F  V  T  H  L  F  L  P  L  -

      GTGTTCCTGACAGGTCTCTGCTCCCCCTTTAACCTGGATGAACATCACCCACGCCTATTC
   61 ---------+---------+---------+---------+---------+---------+ 120
      CACAAGGACTGTCCAGAGACGAGGGGGAAATTGGACCTACTTGTAGTGGGTGCGGATAAG

a     V  F  L  T  G  L  C  S  P  F  N  L  D  E  H  H  P  R  L  F  -

      CCAGGGCCACCAGAAGCTGAATTTGGATACAGTGTCTTACAACATGTTGGGGGTGGACAG
  121 ---------+---------+---------+---------+---------+---------+ 180
      GGTCCCGGTGGTCTTCGACTTAAACCTATGTCACAGAATGTTGTACAACCCCCACCTGTC

a     P  G  P  P  E  A  E  F  G  Y  S  V  L  Q  H  V  G  G  G  Q  -

      CGATGGATGCTGGTGGGCGCCCCCTGGGATGGGCCTTCAGGCGACCGGAGGGGGGACGTT
  181 ---------+---------+---------+---------+---------+---------+ 240
      GCTACCTACGACCACCCGCGGGGGACCCTACCCGGAAGTCCGCTGGCCTCCCCCCTGCAA

a     R  W  M  L  V  G  A  P  W  D  G  P  S  G  D  R  R  G  D  V  -

      TATCGCTGCCCTGTAGGGGGGGCCCACAATGCCCCATGTGCCAAGGGCCACTTAGGTGAC
  241 ---------+---------+---------+---------+---------+---------+ 300
      ATAGCGACGGGACATCCCCCCCGGGTGTTACGGGGTACACGGTTCCCGGTGAATCCACTG

a     Y  R  C  P  V  G  G  A  H  N  A  P  C  A  K  G  H  L  G  D  -

      TACCAACTGGGAAATTCATCTCATCCTGCTGTGAATATGCACCTGGGGATGTCTCTGTTA
  301 ---------+---------+---------+---------+---------+---------+ 360
      ATGGTTGACCCTTTAAGTAGAGTAGGACGACACTTATACGTGGACCCCTACAGAGACAAT

a     Y  Q  L  G  N  S  S  H  P  A  V  N  M  H  L  G  M  S  L  L  -

      GAGACAGATGGTGATGGGGGATTCATGGCCTGTGCCCCTCTCTGGTCTCGTGCTTGTGGC
  361 ---------+---------+---------+---------+---------+---------+ 420
      CTCTGTCTACCACTACCCCCTAAGTACCGGACACGGGGAGAGACCAGAGCACGAACACCG

a     E  T  D  G  D  G  G  F  M  A  C  A  P  L  W  S  R  A  C  G  -

      AGCTCTGTCTTCAGTTCTGGGATATGTGCCCGTGTGGATGCTTCATTCCAGCCTCAGGGA
  421 ---------+---------+---------+---------+---------+---------+ 480
      TCGAGACAGAAGTCAAGACCCTATACACGGGCACACCTACGAAGTAGGTCGGAGTCCCT
```

```
a       S  S  V  F  S  S  G  I  C  A  R  V  D  A  S  F  Q  P  Q  G   -

        AGCCTGGCACCCACTGCCCAACGCTGCCCAACATACATGGATGTTGTCATTGTCTTGGAT
    481 ---------+---------+---------+---------+---------+---------+ 540
        TCGGACCGTGGGTGACGGGTTGCGACGGGTTGTATGTACCTACAACAGTAACAGAACCTA

a       S  L  A  P  T  A  Q  R  C  P  T  Y  M  D  V  V  I  V  L  D   -

        GGCTCCAACAGCATCTACCCCTGGTCTGAAGTTCAGACCTTCCTACGAAGACTGGTAGGG
    541 ---------+---------+---------+---------+---------+---------+ 600
        CCGAGGTTGTCGTAGATGGGGACCAGACTTCAAGTCTGGAAGGATGCTTCTGACCATCCC

a       G  S  N  S  I  Y  P  W  S  E  V  Q  T  F  L  R  R  L  V  G   -

        AAACTGTTTATTGACCCAGAACAGATACAGGTGGGACTGGTACAGTATGGGGAGAGCCCT
    601 ---------+---------+---------+---------+---------+---------+ 660
        TTTGACAAATAACTGGGTCTTGTCTATGTCCACCCTGACCATGTCATACCCCTCTCGGGA

a       K  L  F  I  D  P  E  Q  I  Q  V  G  L  V  Q  Y  G  E  S  P   -

        GTACATGAGTGGTCCCTGGGAGATTTCCGAACGAAGGAAGAAGTGGTGAGAGCAGCAAAG
    661 ---------+---------+---------+---------+---------+---------+ 720
        CATGTACTCACCAGGGACCCTCTAAAGGCTTGCTTCCTTCTTCACCACTCTCGTCGTTTC

a       V  H  E  W  S  L  G  D  F  R  T  K  E  E  V  V  R  A  A  K   -

        AACCTCAGTCGGCGGGAGGGACGAGAAACAAAGACTGCCCAAGCAATAATGGTGGCCTGC
    721 ---------+---------+---------+---------+---------+---------+ 780
        TTGGAGTCAGCCGCCCTCCCTGCTCTTTGTTTCTGACGGGTTCGTTATTACCACCGGACG

a       N  L  S  R  R  E  G  R  E  T  K  T  A  Q  A  I  M  V  A  C   -

        ACAGAAGGGTTCAGTCAGTCCCATGGGGGCCGACCCGAGGCTGCCAGGCTACTGGTGGTT
    781 ---------+---------+---------+---------+---------+---------+ 840
        TGTCTTCCCAAGTCAGTCAGGGTACCCCCGGCTGGGCTCCGACGGTCCGATGACCACCAA

a       T  E  G  F  S  Q  S  H  G  G  R  P  E  A  A  R  L  L  V  V   -

        GTCACTGATGGAGAGTCCCATGATGGAGAGGAGCTTCCTGCAGCACTAAAGGCCTGTGAG
    841 ---------+---------+---------+---------+---------+---------+ 900
        CAGTGACTACCTCTCAGGGTACTACCTCTCCTCGAAGGACGTCGTGATTTCCGGACACTC

a       V  T  D  G  E  S  H  D  G  E  E  L  P  A  A  L  K  A  C  E   -

        GCTGGAAGAGTGACACGCTATGGGATTGCAGTCCTTGGTCACTACCTCCGGCGGCAGCGA
    901 ---------+---------+---------+---------+---------+---------+ 960
        CGACCTTCTCACTGTGCGATACCCTAACGTCAGGAACCAGTGATGGAGGCCGCCGTCGCT

a       A  G  R  V  T  R  Y  G  I  A  V  L  G  H  Y  L  R  R  Q  R   -

        GATCCCAGCTCTTTCCTGAGAGAAATTAGAACTATTGCCAGTGATCCAGATGAGCGATTC
    961 ---------+---------+---------+---------+---------+---------+ 1020
        CTAGGGTCGAGAAAGGACTCTCTTTAATCTTGATAACGGTCACTAGGTCTACTCGCTAAG

a       D  P  S  S  F  L  R  E  I  R  T  I  A  S  D  P  D  E  R  F   -

        TTCTTCAATGTCACAGATGAGGCTGCTCTGACTGACATTGTGGATGCACTAGGAGATCGG
   1021 ---------+---------+---------+---------+---------+---------+ 1080
        AAGAAGTTACAGTGTCTACTCCGACGAGACTGACTGTAACACCTACGTGATCCTCTAGCC

a       F  F  N  V  T  D  E  A  A  L  T  D  I  V  D  A  L  G  D  R   -

        ATTTTTGGCCTTGAAGGGTCCCATGCAGAAAACGAAAGCTCCTTTGGGCTGGAAATGTCT
   1081 ---------+---------+---------+---------+---------+---------+ 1140
        TAAAAACCGGAACTTCCCAGGGTACGTCTTTTGCTTTCGAGGAAACCCGACCTTTACAGA
```

```
a         I  F  G  L  E  G  S  H  A  E  N  E  S  S  F  G  L  E  M  S   -

          CAGATTGGTTTCTCCACTCATCGGCTAAAGGATGGGATTCTTTTTGGGATGGTGGGGGCC
     1141 ---------+---------+---------+---------+---------+---------+ 1200
          GTCTAACCAAAGAGGTGAGTAGCCGATTTCCTACCCTAAGAAAAACCCTACCACCCCCGG

a         Q  I  G  F  S  T  H  R  L  K  D  G  I  L  F  G  M  V  G  A   -

          TATGACTGGGGAGGCTCTGTGCTATGGCTTGAAGGAGGCCACCGCCTTTTCCCCCCACGA
     1201 ---------+---------+---------+---------+---------+---------+ 1260
          ATACTGACCCCTCCGAGACACGATACCGAACTTCCTCCGGTGGCGGAAAAGGGGGGTGCT

a         Y  D  W  G  G  S  V  L  W  L  E  G  G  H  R  L  F  P  P  R   -

          ATGGCACTGGAAGACGAGTTCCCCCCTGCACTGCAGAACCATGCAGCCTACCTGGGTTAC
     1261 ---------+---------+---------+---------+---------+---------+ 1320
          TACCGTGACCTTCTGCTCAAGGGGGGACGTGACGTCTTGGTACGTCGGATGGACCCAATG

a         M  A  L  E  D  E  F  P  P  A  L  Q  N  H  A  A  Y  L  G  Y   -

          TCTGTTTCTTCCATGCTTTTGCGGGGTGGACGCCGCCTGTTTCTCTCTGGGGCTCCTCGA
     1321 ---------+---------+---------+---------+---------+---------+ 1380
          AGACAAAGAAGGTACGAAAACGCCCCACCTGCGGCGGACAAAGAGAGACCCCGAGGAGCT

a         S  V  S  S  M  L  L  R  G  G  R  R  L  F  L  S  G  A  P  R   -

          TTTAGACATCGAGGAAAAGTCATCGCCTTCCAGCTTAAGAAAGATGGGGCTGTGAGGGTT
     1381 ---------+---------+---------+---------+---------+---------+ 1440
          AAATCTGTAGCTCCTTTTCAGTAGCGGAAGGTCGAATTCTTTCTACCCCGACACTCCCAA

a         F  R  H  R  G  K  V  I  A  F  Q  L  K  K  D  G  A  V  R  V   -

          GCCCAGAGCCTCCAGGGGGAGCAGATTGGTTCATACTTTGGCAGTGAGCTCTGCCCATTG
     1441 ---------+---------+---------+---------+---------+---------+ 1500
          CGGGTCTCGGAGGTCCCCCTCGTCTAACCAAGTATGAAACCGTCACTCGAGACGGGTAAC

a         A  Q  S  L  Q  G  E  Q  I  G  S  Y  F  G  S  E  L  C  P  L   -

          GATACAGATAGGGATGGAACAACTGATGTCTTACTTGTGGCTGCCCCCATGTTCCTGGGA
     1501 ---------+---------+---------+---------+---------+---------+ 1560
          CTATGTCTATCCCTACCTTGTTGACTACAGAATGAACACCGACGGGGGTACAAGGACCCT

a         D  T  D  R  D  G  T  T  D  V  L  L  V  A  A  P  M  F  L  G   -

          CCCCAGAACAAGGAAACAGGACGTGTTTATGTGTATCTGGTAGGCCAGCAGTCCTTGCTG
     1561 ---------+---------+---------+---------+---------+---------+ 1620
          GGGGTCTTGTTCCTTTGTCCTGCACAAATACACATAGACCATCCGGTCGTCAGGAACGAC

a         P  Q  N  K  E  T  G  R  V  Y  V  Y  L  V  G  Q  Q  S  L  L   -

          ACCCTCCAAGGAACACTTCAGCCAGAACCCCCCCAGGATGCTCGGTTTGGCTTTGCCATG
     1621 ---------+---------+---------+---------+---------+---------+ 1680
          TGGGAGGTTCCTTGTGAAGTCGGTCTTGGGGGGGTCCTACGAGCCAAACCGAAACGGTAC

a         T  L  Q  G  T  L  Q  P  E  P  P  Q  D  A  R  F  G  F  A  M   -

          GGAGCTCTTCCTGATCTGAACCAAGATGGTTTTGCTGATGTGGCTGTGGGGGCGCCTCTG
     1681 ---------+---------+---------+---------+---------+---------+ 1740
          CCTCGAGAAGGACTAGACTTGGTTCTACCAAAACGACTACACCGACACCCCCGCGGAGAC

a         G  A  L  P  D  L  N  Q  D  G  F  A  D  V  A  V  G  A  P  L   -

          GAAGATGGGCACCAGGGAGCACTGTACCTGTACCATGGAACCCAGAGTGGAGTCAGGCCC
     1741 ---------+---------+---------+---------+---------+---------+ 1800
          CTTCTACCCGTGGTCCCTCGTGACATGGACATGGTACCTTGGGTCTCACCTCAGTCCGGG
```

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a          E  D  G  H  Q  G  A  L  Y  L  Y  H  G  T  Q  S  G  V  R  P   -

           CATCCTGCCCAGAGGATTGCTGCTGCCTCCATGCCACATGCCCTCAGCTACTTTGGCCGA
      1801 ---------+---------+---------+---------+---------+---------+ 1860
           GTAGGACGGGTCTCCTAACGACGACGGAGGTACGGTGTACGGGAGTCGATGAAACCGGCT

a          H  P  A  Q  R  I  A  A  A  S  M  P  H  A  L  S  Y  F  G  R   -

           AGTGTGGATGGTCGGCTAGATCTGGATGGAGATGATCTGGTCGATGTGGCTGTGGGTGCC
      1861 ---------+---------+---------+---------+---------+---------+ 1920
           TCACACCTACCAGCCGATCTAGACCTACCTCTACTAGACCAGCTACACCGACACCCACGG

a          S  V  D  G  R  L  D  L  D  G  D  D  L  V  D  V  A  V  G  A   -

           CAGGGGGCAGCCATCCTGCTCAGCTCCCGGCCCATTGTCCATCTGACCCCATCACTGGAG
      1921 ---------+---------+---------+---------+---------+---------+ 1980
           GTCCCCCGTCGGTAGGACGAGTCGAGGGCCGGGTAACAGGTAGACTGGGGTAGTGACCTC

a          Q  G  A  A  I  L  L  S  S  R  P  I  V  H  L  T  P  S  L  E   -

           GTGACCCCACAGGCCATCAGTGTGGTTCAGAGGGACTGTAGGCGGCGAGGCCAAGAAGCA
      1981 ---------+---------+---------+---------+---------+---------+ 2040
           CACTGGGGTGTCCGGTAGTCACACCAAGTCTCCCTGACATCCGCCGCTCCGGTTCTTCGT

a          V  T  P  Q  A  I  S  V  V  Q  R  D  C  R  R  R  G  Q  E  A   -

           GTCTGTCTGACTGCAGCCCTTTGCTTCCAAGTGACCTCCCGTACTCCTGGTCGCTGGGAT
      2041 ---------+---------+---------+---------+---------+---------+ 2100
           CAGACAGACTGACGTCGGGAAACGAAGGTTCACTGGAGGGCATGAGGACCAGCGACCCTA

a          V  C  L  T  A  A  L  C  F  Q  V  T  S  R  T  P  G  R  W  D   -

           CACCAATTCTACATGAGGTTCACCGCATCACTGGATGAATGGACTGCTGGGGCACGTGCA
      2101 ---------+---------+---------+---------+---------+---------+ 2160
           GTGGTTAAGATGTACTCCAAGTGGCGTAGTGACCTACTTACCTGACGACCCCGTGCACGT

a          H  Q  F  Y  M  R  F  T  A  S  L  D  E  W  T  A  G  A  R  A   -

           GCATTTGATGGCTCTGGCCAGAGGTTGTCCCCTCGGAGGCTCCGGCTCAGTGTGGGGAAT
      2161 ---------+---------+---------+---------+---------+---------+ 2220
           CGTAAACTACCGAGACCGGTCTCCAACAGGGGAGCCTCCGAGGCCGAGTCACACCCCTTA

a          A  F  D  G  S  G  Q  R  L  S  P  R  R  L  R  L  S  V  G  N   -

           GTCACTTGTGAGCAGCTACACTTCCATGTGCTGGATACATCAGATTACCTCCGGCCAGTG
      2221 ---------+---------+---------+---------+---------+---------+ 2280
           CAGTGAACACTCGTCGATGTGAAGGTACACGACCTATGTAGTCTAATGGAGGCCGGTCAC

a          V  T  C  E  Q  L  H  F  H  V  L  D  T  S  D  Y  L  R  P  V   -

           GCCTTGACTGTGACCTTTGCCTTGGACAATACTACAAAGCCAGGGCCTGTGCTGAATGAG
      2281 ---------+---------+---------+---------+---------+---------+ 2340
           CGGAACTGACACTGGAAACGGAACCTGTTATGATGTTTCGGTCCCGGACACGACTTACTC

a          A  L  T  V  T  F  A  L  D  N  T  T  K  P  G  P  V  L  N  E   -

           GGCTCACCCACCTCTATACAAAAGCTGGTCCCCTTCTCAAAGGATTGTGGCCCTGACAAT
      2341 ---------+---------+---------+---------+---------+---------+ 2400
           CCGAGTGGGTGGAGATATGTTTTCGACCAGGGGAAGAGTTTCCTAACACCGGGACTGTTA

a          G  S  P  T  S  I  Q  K  L  V  P  F  S  K  D  C  G  P  D  N   -

           GAATGTGTCACAGACCTGGTGCTTCAAGTGAATATGGACATCAGAGGCTCCAGGAAGGCC
      2401 ---------+---------+---------+---------+---------+---------+ 2460
           CTTACACAGTGTCTGGACCACGAAGTTCACTTATACCTGTAGTCTCCGAGGTCCTTCCGG
```

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a           E  C  V  T  D  L  V  L  Q  V  N  M  D  I  R  G  S  R  K  A   -

           CCATTTGTGGTTCGAGGTGGCCGGCGGAAAGTGCTGGTATCTACAACTCTGGAGAACAGA
      2461 ---------+---------+---------+---------+---------+---------+ 2520
           GGTAAACACCAAGCTCCACCGGCCGCCTTTCACGACCATAGATGTTGAGACCTCTTGTCT

a           P  F  V  V  R  G  G  R  R  K  V  L  V  S  T  T  L  E  N  R   -

           AAGGAAAATGCTTACAATACGAGCCTGAGTATCATCTTCTCTAGAAACCTCCACCTGGCC
      2521 ---------+---------+---------+---------+---------+---------+ 2580
           TTCCTTTTACGAATGTTATGCTCGGACTCATAGTAGAAGAGATCTTTGGAGGTGGACCGG

a           K  E  N  A  Y  N  T  S  L  S  I  I  F  S  R  N  L  H  L  A   -

           AGTCTCACTCCTCAGAGAGAGAGCCCAATAAAGGTGGAATGTGCCGCCCCTTCTGCTCAT
      2581 ---------+---------+---------+---------+---------+---------+ 2640
           TCAGAGTGAGGAGTCTCTCTCTCGGGTTATTTCCACCTTACACGGCGGGGAAGACGAGTA

a           S  L  T  P  Q  R  E  S  P  I  K  V  E  C  A  A  P  S  A  H   -

           GCCCGGCTCTGCAGTGTGGGGCATCCTGTCTTCCAGACTGGAGCCAAGGTGACCTTTCTG
      2641 ---------+---------+---------+---------+---------+---------+ 2700
           CGGGCCGAGACGTCACACCCCGTAGGACAGAAGGTCTGACCTCGGTTCCACTGGAAAGAC

a           A  R  L  C  S  V  G  H  P  V  F  Q  T  G  A  K  V  T  F  L   -

           CTAGAGTTTGAGTTTAGCTGCTCCTCTCTCCTGAGCCAGGTCTTTGGGAAGCTGACTGCC
      2701 ---------+---------+---------+---------+---------+---------+ 2760
           GATCTCAAACTCAAATCGACGAGGAGAGAGGACTCGGTCCAGAAACCCTTCGACTGACGG

a           L  E  F  E  F  S  C  S  S  L  L  S  Q  V  F  G  K  L  T  A   -

           AGCAGTGACAGCCTGGAGAGAAATGGCACCCTTCAAGAAAACACAGCCCAGACCTCAGCC
      2761 ---------+---------+---------+---------+---------+---------+ 2820
           TCGTCACTGTCGGACCTCTCTTTACCGTGGGAAGTTCTTTTGTGTCGGGTCTGGAGTCGG

a           S  S  D  S  L  E  R  N  G  T  L  Q  E  N  T  A  Q  T  S  A   -

           TACATCCAATATGAGCCCCACCTCCTGTTCTCTAGTGAGTCTACCCTGCACCGCTATGAG
      2821 ---------+---------+---------+---------+---------+---------+ 2880
           ATGTAGGTTATACTCGGGGTGGAGGACAAGAGATCACTCAGATGGGACGTGGCGATACTC

a           Y  I  Q  Y  E  P  H  L  L  F  S  S  E  S  T  L  H  R  Y  E   -

           GTTCACCCATATGGGACCCTCCCAGTGGGTCCTGGCCCAGAATTCAAAACCACTCTCAGG
      2881 ---------+---------+---------+---------+---------+---------+ 2940
           CAAGTGGGTATACCCTGGGAGGGTCACCCAGGACCGGGTCTTAAGTTTTGGTGAGAGTCC

a           V  H  P  Y  G  T  L  P  V  G  P  G  P  E  F  K  T  T  L  R   -

           ACTAACAATGCAAGCTGCATAGTGCAGAACCTGACTGAACCCCCAGGCCCACCTGTGCAT
      2941 ---------+---------+---------+---------+---------+---------+ 3000
           TGATTGTTACGTTCGACGTATCACGTCTTGGACTGACTTGGGGGTCCGGGTGGACACGTA

a           T  N  N  A  S  C  I  V  Q  N  L  T  E  P  P  G  P  P  V  H   -

           CCAGAGGAGCTTCAACACACAAACAGACTGAATGGGAGCAATACTCAGTGTCAGGTGGTG
      3001 ---------+---------+---------+---------+---------+---------+ 3060
           GGTCTCCTCGAAGTTGTGTGTTTGTCTGACTTACCCTCGTTATGAGTCACAGTCCACCAC

a           P  E  E  L  Q  H  T  N  R  L  N  G  S  N  T  Q  C  Q  V  V   -

           AGGTGCCACCTTGGGCAGCTGGCAAAGGGGACTGAGGTCTCTGTTGGACTATTGAGGCTG
      3061 ---------+---------+---------+---------+---------+---------+ 3120
           TCCACGGTGGAACCCGTCGACCGTTTCCCCTGACTCCAGAGACAACCTGATAACTCCGAC
```

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a       R  C  H  L  G  Q  L  A  K  G  T  E  V  S  V  G  L  L  R  L   -

        GTTCACAATGAATTTTTCCGAAGAGCCAAGTTCAAGTCCCTGACGGTGGTCAGCACCTTT
   3121 ---------+---------+---------+---------+---------+---------+ 3180
        CAAGTGTTACTTAAAAAGGCTTCTCGGTTCAAGTTCAGGGACTGCCACCAGTCGTGGAAA

a       V  H  N  E  F  F  R  R  A  K  F  K  S  L  T  V  V  S  T  F   -

        GAGCTGGGAACCGAAGAGGGCAGTGTCCTACAGCTGACTGAAGCCTCCCGTTGGAGTGAG
   3181 ---------+---------+---------+---------+---------+---------+ 3240
        CTCGACCCTTGGCTTCTCCCGTCACAGGATGTCGACTGACTTCGGAGGGCAACCTCACTC

a       E  L  G  T  E  E  G  S  V  L  Q  L  T  E  A  S  R  W  S  E   -

        AGCCTCTTGGAGGTGGTTCAGACCCGGCCTATCCTCATCTCCCTGTGGATCCTCATAGGC
   3241 ---------+---------+---------+---------+---------+---------+ 3300
        TCGGAGAACCTCCACCAAGTCTGGGCCGGATAGGAGTAGAGGGACACCTAGGAGTATCCG

a       S  L  L  E  V  V  Q  T  R  P  I  L  I  S  L  W  I  L  I  G   -

        AGTGTCCTGGGAGGGTTGCTCCTGCTTGCTCTCCTTGTCTTCTGCCTGTGGAAGCTTGGC
   3301 ---------+---------+---------+---------+---------+---------+ 3360
        TCACAGGACCCTCCCAACGAGGACGAACGAGAGGAACAGAAGACGGACACCTTCGAACCG

a       S  V  L  G  G  L  L  L  L  A  L  L  V  F  C  L  W  K  L  G   -

        TTCTTTGCCCATAAGAAAATCCCTGAGGAAGAAAAAAGAGAAGAGAAGTTGGAGCAATGA
   3361 ---------+---------+---------+---------+---------+---------+ 3420
        AAGAAACGGGTATTCTTTTAGGGACTCCTTCTTTTTTCTCTTCTCTTCAACCTCGTTACT

a       F  F  A  H  K  K  I  P  E  E  E  K  R  E  E  K  L  E  Q

        ATGTAGAATAAGGGTCTAGAAAGTCCTCCCTGGCAGCTTTCTTCAAGAGACTTGCATAAA
   3421 ---------+---------+---------+---------+---------+---------+ 3480
        TACATCTTATTCCCAGATCTTTCAGGAGGGACCGTCGAAAGAAGTTCTCTGAACGTATTT

        AGCAGAGGTTTGGGGGCTCAGATGGGACAAGAAGCCGCCTCTGGACTATCTCCCCAGACC
   3481 ---------+---------+---------+---------+---------+---------+ 3540
        TCGTCTCCAAACCCCCGAGTCTACCCTGTTCTTCGGCGGAGACCTGATAGAGGGGTCTGG

        AGCAGCCTGACTTGACTTTTGAGTCCTAGGGATGCTGCTGGCTAGAGATGAGGCTTTACC
   3541 ---------+---------+---------+---------+---------+---------+ 3600
        TCGTCGGACTGAACTGAAAACTCAGGATCCCTACGACGACCGATCTCTACTCCGAAATGG

        TCAGACAAGAAGAGCTGGCACCAAAACTAGCCATGCTCCCACCCTCTGCTTCCCTCCTCC
   3601 ---------+---------+---------+---------+---------+---------+ 3660
        AGTCTGTTCTTCTCGACCGTGGTTTTGATCGGTACGAGGGTGGGAGACGAAGGGAGGAGG

        TCGTGATCCTGGTTCCATAGCCAACACTGGGGCTTTTGTTTGGGGTCCTTTTATCCCCAG
   3661 ---------+---------+---------+---------+---------+---------+ 3720
        AGCACTAGGACCAAGGTATCGGTTGTGACCCCGAAAACAAACCCCAGGAAAATAGGGGTC

        GAATCAATAATTTTTTTGCCTAGGAAAAAAAAAAGCGGCCGCGAATTCGATATCAAGCT
   3721 ---------+---------+---------+---------+---------+--------- 3779
        CTTAGTTATTAAAAAAACGGATCCTTTTTTTTTTCGCCGGCGCTTAAGCTATAGTTCGA
```

(2) INFORMATION FOR SEQ ID NO. 3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 143 base pairs
(B) TYPE: nucleic acid and amino acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(iii) MOLECULAR TYPE: cDNA
(vi) ORIGINAL SOURCE:
(A) ORGANISM: human
(B) CELLTYPE: chondrocyte

(xi) SEQUENCE DESCRIPTION: SEQ ID NO. 3:

```
            NdeI
              |
      GGGGCATATGGTTCAGAACCTGGGTTGCTACGTTGTTTCCGGTCTGATCATCTCCGCTCT
    1 ---------+---------+---------+---------+---------+---------+ 60
      CCCCGTATACCAAGTCTTGGACCCAACGATGCAACAAAGGCCAGACTAGTAGAGGCGAGA

b       G  H  M  V  Q  N  L  G  C  Y  V  V  S  G  L  I  I  S  A  L  -

      GCTGCCGGCTGTTGCTCACGGTGGTAACTACTTCCTAAGCTTGTCCCAGGTTATCAGCGG
   61 ---------+---------+---------+---------+---------+---------+ 120
      CGACGGCCGACAACGAGTGCCACCATTGATGAAGGATTCGAACAGGGTCCAATAGTCGCC

b       L  P  A  V  A  H  G  G  N  Y  F  L  S  L  S  Q  V  I  S  G  -

                BamHI
                  |
      CCTGGTGCCGCGCGGATCCCCCC
  121 ---------+---------+--- 143
      GGACCACGGCGCGCCTAGGGGGG

b       L  V  P  R  G  S  P    -
```

CLAIMS

1. A recombinant or isolated collagen binding integrin subunit α10 comprising essentially the amino acid sequence shown in SEQ ID No. 1 or SEQ ID No. 2, or homologues or fragments thereof having essentially the same biological activity.

2. A process of producing a recombinant integrin subunit α10 comprising essentially the amino acid sequence shown in SEQ ID No. 1 or SEQ ID No. 2, or homologues or fragments thereof having essentially the same biological activity, which process comprises the steps of

a) isolating a polynucleotide comprising a nucleotide sequence coding for an integrin subunit α10, or homologues or fragments thereof having essentially the same biological activity,

b) constructing an expression vector comprising the isolated polynucleotide,

c) transforming a host cell with said expression vector,

d) culturing said transformed host cell in a culture medium under conditions suitable for expression of integrin subunit α10, or homologues or fragments thereof having essentially the same biological activity, in said transformed host cell, and, optionally,

e) isolating the integrin subunit α10, or homologues or fragments thereof having essentially the same biological activity, from said transformed host cell or said culture medium.

3. A process of providing an integrin subunit α10, or homologues or fragments thereof having essentially the same biological activity, whereby said subunit is isolated from a cell in which it is naturally present.

4. An isolated polynucleotide comprising a nucleotide coding for an integrin subunit α10, or for homologues or fragments thereof having essentially the same

biological activity, which polynucleotide comprises essentially the nucleotide sequence shown in SEQ ID No. 1 or SEQ ID No. 2 or suitable parts thereof.

5. An isolated polynucleotide or oligonucleotide which hybridises to a DNA or RNA coding for an integrin subunit α10, or for homologues or fragments thereof having essentially the same biological activity, wherein said polynucleotide or oligonucleotide fails to hybridise to a DNA or RNA encoding an integrin subunit α1.

6. A vector comprising a polynucleotide or oligonucleotide coding for an integrin subunit α10, or for homologues or fragments thereof having essentially the same biological acitivty, which polynucleotide or oligonucleotide comprises essentially the nucleotide sequence shown in SEQ ID No. 1 or SEQ ID No. 2 or parts thereof.

7. A vector comprising a polynucleotide or oligonucleotide which hybridises to a DNA or RNA coding for an integrin subunit α10, or for homologues or fragments thereof, wherein said polynucleotide or oligonucleotide fails to hybridise to a DNA or RNA encoding an integrin subunit α1.

8. A cell containing the vector as defined in any one of claims 6 and 7.

9. A cell generated by steps a) to d) of the process as defined in claim 2, in which a polynucleotide or oligonucleotide coding for an integrin subunit α10, or for homologues or fragments thereof having essentially the same biological acitivity, which polynucleotide or oligonucleotide comprises the nucleotide sequence shown in SEQ ID No. 1 or SEQ ID No. 2 or parts thereof, has been stably integrated in the cell genome.

10. Binding entities having the capability of binding specifically to an integrin subunit α10 comprising the amino acid sequence of SEQ ID No. 1 or SEQ ID No. 2, or to homologues or fragments thereof.

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11. Binding entities according to claim 10, which are chosen from the group comprising proteins, peptides, carbohydrates, lipids, natural integrin binding ligands, and fragments thereof.

12. Binding entities according to claim 10, which are polyclonal or monoclonal antibodies, or fragments thereof.

13. A recombinant or isolated integrin heterodimer comprising a subunit α10 and a subunit β, in which the subunit α10 comprises essentially the amino acid sequence shown in SEQ ID No. 1 or SEQ ID No. 2, and homologues and fragments thereof having essentially the same biological activity.

14. A recombinant or isolated integrin heterodimer according to claim 13, wherein the subunit β is β1.

15. A process of producing a recombinant integrin heterodimer comprising a subunit α10 and a subunit β, in which the subunit α10 comprises essentially the amino acid sequence shown in SEQ ID No. 1 or SEQ ID No. 2, and homologues and fragments thereof having essentially the same biological activity, which process comprises the steps of

a) isolating one polynucleotide comprising a nucleotide sequence coding for a subunit α10 of an integrin heterodimer and, optionally, another polynucleotide comprising a nucleotide sequence coding for a subunit β of an integrin heterodimer, or polynucleotides or oligonucleotides coding for homologues or fragments thereof having essentially the same biological activity,

b) constructing an expression vector comprising said isolated polynucleotide coding for said subunit α10 optionally in combination with an expression vector comprising said isolated nucleotide coding for said subunit β,

c) transforming a host cell with said expression vector or vectors,

d) culturing said transformed host cell in a culture medium under conditions suitable for expression of an integrin heterodimer comprising a subunit α10 and a subunit β, or homologues or fragments thereof having essentially the same biological activity, in said transformed host cell, and, optionally,

e) isolating the integrin heterodimer comprising a subunit α10 and a subunit β, or homologues or fragments thereof having essentially the same biological activity, or the α10 subunit thereof from said transformed host cell or said culture medium.

16. A process of providing a integrin heterodimer comprising a subunit α10 and a subunit β, or homologues or fragments thereof having essentially the same biological activity, whereby said integrin heterodimer is isolated from a cell in which it is naturally present.

17. A cell containing a first vector, said first vector comprising a polynucleotide or oligonucleotide coding for a subunit α10 of an integrin heterodimer, or for homologues or parts thereof having essentially the same biological activity, which polynucleotide or oligonucleotide comprises essentially the nucleotide sequence shown in SEQ ID No. 1 or SEQ ID No. 2 or parts thereof, and a second vector, said second vector comprising a polynucleotide or oligonucleotide coding for a subunit β of an integrin heterodimer, or for homologues or fragments thereof having essentially the same biological activity.

18. Binding entities having the capability of binding specifically to an integrin heterodimer comprising a subunit α10 and a subunit β, or to homologues or fragments thereof having essentially the same biological activity, or an subunit α10 thereof, having essentially the same biological activity.

19. Binding entities according to claim 18, wherein the subunit β is β1.

20. Binding entities according to claim 18 or 19, which are chosen among the group comprising proteins, peptides, carbohydrates, lipids, natural integrin binding ligands, and fragments thereof.

21. Binding entities according to claim 18 or 19, which are polyclonal or monoclonal antibodies

22. A fragment of the integrin subunit α10, which fragment is a peptide chosen from the group comprising peptides of the cytoplasmic domain, the I-domain and the spliced domain.

23. A fragment according to claim 22, which is a peptide comprising the amino acid sequence KLGFFAHKKIPEEEKREEKLEQ.

24. A fragment according to claim 22, which comprises the amino acid sequence from about amino acid No. 952 to about amino acid no. 986 of SEQ ID No. 1.

25. A fragment according to claim 22, which is a peptide comprising the amino acid sequence from about amino acid No. 140 to about amino acid no. 337 of SEQ ID No. 1.

26. A method of producing a fragment of the integrin subunit α10 as defined in any one of claims 22-25, which method comprises a sequential addition of amino acids containing protective groups.

27. A polynucleotide or oligonucleotide coding for a fragment of the integrin subunit α10 as defined in any one of claims 22-25.

28. Binding entities having the capability of binding specifically to a fragment of the human integrin subunit α10 as defined in any one of claims 22-25.

29. Binding entities according to claim 28, which are chosen from the group comprising proteins, peptides, carbohydrates, lipids, natural integrin binding ligands, and fragments thereof.

30. Binding entities according to claim 28, which are polyclonal or monoclonal antibodies, or fragments thereof.

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31. An *in vitro* process of using an integrin subunit α10 comprising the amino acid sequence shown in SEQ ID No. 1 or SEQ ID No. 2, or an integrin heterodimer comprising said subunit α10 and a subunit β, or a homologue or fragment of said integrin or subunit having essentially the same biologically activity, as a marker or target molecule of cells or tissues expressing said integrin subunit α10, which cells or tissues are of animal including human origin.

32. An *in vitro* process according to claim 31, whereby said fragment is a peptide chosen from the group comprising peptides of the cytoplasmic domain, the I-domain and the spliced domain.

33. An *in vitro* process according to claim 31, whereby said fragment is a peptide comprising the amino acid sequence KLGFFAHKKIPEEEKREEKLEQ.

34. An *in vitro* process according to claim 31, whereby said fragment comprises the amino acid sequence from about amino acid no. 952 to about amino acid no. 986 of SEQ ID No. 1.

35. An *in vitro* process according to claim 31, whereby said fragment comprises the amino acid sequence from about amino acid no. 140 to about amino acid no. 337 of SEQ ID No. 1.

36. An *in vitro* process according to claim 31, whereby the subunit β is β1.

37. An *in vitro* process according to claim 31, whereby said cells are chosen from the group comprising chondrocytes, smooth muscle cells, endothelial cells, osteoblasts and fibroblasts.

38. An *in vitro* process according to any one of claims 31-37, which process is used during pathological conditions involving said subunit α10.

39. An *in vitro* process according to claim 38, which pathological conditions comprise damage of cartilage.

40. An *in vitro* process according to claim 38, which pathological conditions comprise trauma, rheumatoid arthritis and osteoarthritis.

41. An *in vitro* process according to any one of claims 31-37, which is a process for detecting the formation of cartilage during embryonal development.

42. An *in vitro* process according to any one of claims 31-37, which is a process for detecting physiological or therapeutic reparation of cartilage.

43. An *in vitro* process according to any one of claims 31-37, which is a process for selection and analysis, or for sorting, isolating or purification of chondrocytes.

44. An *in vitro* process according to any one of claims 31-37, which is a process for detecting regeneration of cartilage or chondrocytes during transplantation of cartilage or chondrocytes.

45. A process according to any one of claims 31-37, which is a process for in vitro studies of differentiation of chondrocytes.

46. An *in vitro* process of using binding entities having the capability of binding specifically to an integrin subunit α10 comprising the amino acid sequence shown in SEQ ID No. 1 or SEQ ID No. 2, or an integrin heterodimer comprising said subunit α10 and a subunit β, or to homologues or fragments thereof having essentially the same biological activity, as markers or target molecules of cells or tissues expressing said integrin subunit α10, which cells or tissues are of animal including human origin.

47. An *in vitro* process according to claim 46, whereby said fragment is a peptide chosen from the group comprising peptides of the cytoplasmic domain, the I-domain and the spliced domain.

48. An *in vitro* process according to claim 46, whereby said fragment is a peptide comprising the amino acid sequence KLGFFAHKKIPEEEKREEKLEQ.

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49. An *in vitro* process according to claim 46, whereby said fragment comprises the amino acid sequence from about amino acid no. 952 to about amino acid no. 986 of SEQ ID No. 1.

50. An *in vitro* process according to claim 46, whereby said fragment comprises the amino acid sequence from about amino acid no. 140 to about amino acid No. 337 of SEQ ID No. 1.

51. An *in vitro* process according to claim 46, whereby the subunit β is β1.

52. An *in vitro* process according to any one of claims 46-51, which is a process for detecting the presence of an integrin subunit α10 comprising the amino acid sequence shown in SEQ ID No. 1 or SEQ ID No. 2, or of an integrin heterodimer comprising said subunit α10 and a subunit β, or of homologues or fragments thereof having essentially the same biological activity.

53. An *in vitro* process according to any one of claims 46-51, which process is a process for determining the differentiation-state of cells during embryonic development, angiogenesis, or development of cancer.

54. An *in vitro* process for detecting the presence of a integrin subunit α10, or of a homologue or fragment of said integrin subunit having essentially the same biological activity, on cells, whereby a polynucleotide or oligonucleotide chosen from the group comprising a polynucleotide or oligonucleotide shown in SEQ ID No. 1 is used as a marker under hybridisation conditions wherein said polynucleotide or oligonucleotide fails to hybridise to a DNA or RNA encoding an integrin subunit α1.

55. An *in vitro* process according to claim 54, whereby said cells are chosen from the group comprising chondrocytes, smooth muscle cells, endothelial cells, osteoblasts and fibroblasts.

56. An *in vitro* process according to claim 54, whereby said fragment is a peptide chosen from the group

comprising peptides of the cytoplasmic domain, the I-domain and the spliced domain.

57. An *in vitro* process according to claim 54, whereby said fragment is a peptide comprising the amino acid sequence KLGFFAHKKIPEEEKREEKLEQ.

58. An *in vitro* process according to claim 54, whereby said fragment comprises the amino acid sequence from about amino acid No. 952 to about amino acid no. 986 of SEQ ID No. 1.

59. An *in vitro* process according to claim 54, whereby said fragment comprises the amino acid sequence from about amino acid No. 140 to about amino acid No. 337 of SEQ ID No. 1.

60. An *in vitro* process according to any one of claims 54-59, which is a process for determining the differentiation-state of cells during development, in pathological conditions, in tissue regeneration or in therapeutic and physiological reparation of cartilage.

61. An *in vitro* process according to claim 60, wherein the pathological conditions are any pathological conditions involving the integrin subunit $\alpha10$.

62. An *in vitro* process according to claim 61, whereby said pathological conditions are rheumatoid arthritis, osteoarthrosis or cancer.

63. An *in vitro* process according to claim 60, whereby said cells are chosen from the group comprising chondrocytes, smooth muscle cells, endothelial cells, osteoblasts and fibroblasts.

64. An *in vitro* process for determining the differentiation-state of cells during development, in pathological conditions, in tissue regeneration and in therapeutic and physiological reparation of cartilage, whereby a polynucleotide or oligonucleotide chosen from the nucleotide sequence shown in SEQ ID No. 1 is used as a marker under hybridisation conditions wherein said polynucleotide or oligonucleotide fails to hybridise to a DNA or RNA encoding an integrin subunit $\alpha1$.

65. An *in vitro* process according to claim 64, whereby said polynucleotide or oligonucleotide is a polynucleotide or oligonucleotide coding for a peptide chosen from the group comprising peptides of the cytoplasmic domain, the I-domain and the spliced domain.

66. An *in vitro* process according to claim 65, whereby said polynucleotide or oligonucleotide is a polynucleotide or oligonucleotide coding for a peptide comprising the amino acid sequence KLGFFAHKKIPEEEKREEKLEQ.

67. An *in vitro* process according to claim 65, whereby said peptide comprises the amino acid sequence from about amino acid no. 952 to about amino acid no. 986 of SEQ ID No. 1.

68. An *in vitro* process according to claim 65, whereby said peptide comprises the amino acid sequence from about amino acid no. 140 to about amino acid no. 337 of SEQ ID No. 1.

69. An *in vitro* process according to claim 65, whereby said pathological conditions are any pathological conditions involving the integrin subunit $\alpha 10$.

70. An *in vitro* process according to claim 69, whereby said pathological conditions are rheumatoid arthritis, osteoarthrosis or cancer.

71. An *in vitro* process according to claim 69, whereby said pathological conditions are atherosclerosis or inflammation.

72. An *in vitro* process according to any one of claims 64-71, whereby said cells are chosen from the group comprising chondrocytes, smooth muscle cells, endothelial cells, osteoblasts and fibroblasts.

73. A pharmaceutical composition comprising as an active ingredient a pharmaceutical agent or an antibody which is capable of using an integrin heterodimer comprising a subunit $\alpha 10$ and a subunit β, or the subunit $\alpha 10$ thereof, or a homologue or fragment of said integrin or

subunit α10 having essentially the same biological activity, as a target molecule.

74. A pharmaceutical composition according to claim 73, for use in stimulating, inhibiting or blocking the formation of cartilage, bone or blood vessels.

75. A pharmaceutical composition according to claim 73, for use in preventing adhesion between tendon/ligaments and the surrounding tissue after infection, inflammation and after surgical intervention where adhesion impairs the function of the tissue.

76. A vaccine comprising as an active ingredient an integrin heterodimer comprising a subunit α10 and a subunit β, or the subunit α10 thereof, or a homologue or fragment of said integrin or subunit α10, or DNA or RNA coding for said integrin subunit α10.

77. *In vitro* use of the integrin subunit α10 as a marker or target in transplantation of cartilage or chondrocytes.

78. An *in vitro* method of using binding entities having the capability of binding specifically to an integrin subunit α10 comprising the amino acid sequence shown in SEQ ID No. 1 or SEQ ID No. 2, or an integrin heterodimer comprising said subunit α10 and a subunit β, or to homologues or fragments thereof having essentially the same biological activity, for promoting adhesion of chondrocytes and/or osteoblasts to surfaces of implants to stimulate osseointegration.

79. A method of *in vitro* detecting the presence of integrin binding entities, comprising interaction of an integrin heterodimer comprising a subunit α10 and a subunit β, or the subunit α10 thereof, or a homologue or fragment of said integrin or subunit having essentially the same biological activity, with a sample, thereby causing said integrin, subunit α10, or homologue or fragment thereof, to modulate the binding to its natural ligand or other integrin binding proteins present in said sample.

80. A method of *in vitro* studying consequences of the interaction of a human heterodimer integrin comprising a subunit α10 and a subunit β, or the subunit α10 thereof, or a homologue or fragment of said integrin or subunit having essentially the same biological activity, with an integrin binding entity and thereby initiate a cellular reaction.

81. A method according to claim 80, whereby the consequences of said interactions are measured as alterations in cellular functions.

82. An *in vitro* method of using DNA or RNA encoding an integrin subunit α10 or homologues or fragments thereof as a target molecule.

83. An *in vitro* method according to claim 82, whereby a polynucleotide or oligonucleotide hybridises to the DNA or RNA encoding an integrin subunit α10, or homologues or fragments thereof having essentially the same biological activity, and whereby said polynucleotide or oligonucleotide fails to hybridise to a DNA or RNA encoding an integrin subunit α1.

84. An *in vitro* method of using a human heterodimer integrin comprising a subunit α10 and a subunit β, or the subunit α10 thereof, or a homologue or fragment of said integrin or subunit, or a DNA or RNA encoding an integrin subunit α10 or homologues or fragments thereof, as a marker or target molecule during angiogenesis.

85. A pharmaceutical composition comprising as an active ingredient a pharmaceutical agent or an antibody which is capable of stimulating cell surface expression of an integrin heterodimer comprising a subunit α10 and a subunit β, or the subunit α10 thereof, or a homologue or fragment of said integrin or subunit α10 having essentially the same biological activity.

86. A process of using a collagen binding integrin subunit α10 comprising the amino acid sequence shown in SEQ ID No. 1 or SEQ ID No. 2, or an integrin heterodimer comprising said subunit α10 and a subunit β, or a

homologue or fragment of said integrin or subunit having essentially the same biologically activity, as a marker or target molecule of cells or tissues expressing said integrin subunit α10, which cells or tissues are of animal including human origin.

87. A process according to claim 86, whereby said fragment is a peptide chosen from the group comprising peptides of the cytoplasmic domain, the I-domain and the spliced domain.

88. A process according to claim 86, whereby said fragment is a peptide comprising the amino acid sequence KLGFFAHKKIPEEEKREEKLEQ.

89. A process according to claim 86, whereby said fragment comprises the amino acid sequence from about amino acid no. 952 to about amino acid no. 986 of SEQ ID No. 1.

90. A process according to claim 86, whereby said fragment comprises the amino acid sequence from about amino acid no. 140 to about amino acid no. 337 of SEQ ID No. 1.

91. A process according to claim 86, whereby the subunit β is β1.

92. A process according to claim 86, whereby said cells are chosen from the group comprising chondrocytes, smooth muscle cells, endothelial cells, osteoblasts and fibroblasts.

93. A process according to any one of claims 86-92, which process is used during pathological conditions involving said subunit α10.

94. A process according to claim 93, which pathological conditions comprise damage of cartilage.

95. A process according to claim 93, which pathological conditions comprise trauma, rheumatoid arthritis and osteoarthritis.

96. A process according to any one of claims 86-92, which is a process for detecting the formation of cartilage during embryonal development.

97. A process according to any one of claims 86-92, which is a process for detecting physiological or therapeutic reparation of cartilage.

98. A process according to any one of claims 86-92, which is a process for detecting regeneration of cartilage or chondrocytes during transplantation of cartilage or chondrocytes.

99. A process of using binding entities having the capability of binding specifically to an integrin subunit $\alpha10$ comprising the amino acid sequence shown in SEQ ID No. 1 or SEQ ID No. 2, or an integrin heterodimer comprising said subunit $\alpha10$ and a subunit β, or to homologues or fragments thereof having essentially the same activity, as markers or target molecules of cells or tissues expressing said integrin subunit $\alpha10$, which cells or tissues are of animal including human origin.

100. A process according to claim 99, whereby said fragment is a peptide chosen from the group comprising peptides of the cytoplasmic domain, the I-domain and the spliced domain.

101. A process according to claim 99, whereby said fragment is a peptide comprising the amino acid sequence KLGFFAHKKIPEEEKREEKLEQ.

102. A process according to claim 99, whereby said fragment comprises the amino acid sequence from about amino acid no. 952 to about amino acid no. 986 of SEQ ID No. 1.

103. A process according to claim 99, whereby said fragment comprises the amino acid sequence from about amino acid no. 140 to about amino acid No. 337 of SEQ ID No. 1.

104. A process according to claim 99, whereby the subunit β is $\beta1$.

105. A process according to any one of claims 99-104, which is a process for detecting the presence of an integrin subunit $\alpha10$ comprising the amino acid sequence shown in SEQ ID No. 1 or SEQ ID No. 2, or of an integrin

heterodimer comprising said subunit α10 and a subunit β, or of homologues or fragments thereof having essentially the same biologically activity.

106. A process according to any one of claims 99-104, which process is a process for determining the differentiation-state of cells during embryonic development, angiogenesis, or development of cancer.

107. A process for detecting the presence of an integrin subunit α10, or of a homologue or fragment of said integrin subunit having essentially the same activity, on cells, whereby a polynucleotide or oligonucleotide chosen from the group comprising a polynucleotide or oligonucleotide shown in SEQ ID No. 1 is used as a marker under hybridisation conditions wherein said polynucleotide or oligonucleotide fails to hybridise to a DNA or RNA encoding an integrin subunit α1.

108. A process according to claim 107, whereby said cells are chosen from the group comprising chondrocytes, smooth muscle cells, endothelial cells, osteoblasts and fibroblasts.

109. A process according to claim 107, whereby said fragment is a peptide chosen from the group comprising peptides of the cytoplasmic domain, the I-domain and the spliced domain.

110. A process according to claim 107, whereby said fragment is a peptide comprising the amino acid sequence KLGFFAHKKIPEEEKREEKLEQ.

111. A process according to claim 107, whereby said fragment comprises the amino acid sequence from about amino acid No. 952 to about amino acid no. 986 of SEQ ID No. 1.

112. A process according to claim 107, whereby said fragment comprises the amino acid sequence from about amino acid No. 140 to about amino acid No. 337 of SEQ ID No. 1.

113. A process according to any one of claims 107-112, which is a process for determining the differentiation-state of cells during development, in pathological conditions, in tissue regeneration or in therapeutic and physiological reparation of cartilage.

114. A process according to claim 113, wherein the pathological conditions are any pathological conditions involving the integrin subunit α10.

115. A process according to claim 113, whereby said pathological conditions are rheumatoid arthritis, osteoarthrosis or cancer.

116. A process according to claim 113, whereby said cells are chosen from the group comprising chondrocytes, smooth muscle cells, endothelial cells, osteoblasts and fibroblasts.

117. A process for determining the differentiation-state of cells during development, in pathological conditions, in tissue regeneration and in therapeutic and physiological reparation of cartilage, whereby a polynucleotide or oligonucleotide chosen from the nucleotide sequence shown in SEQ ID No. 1 is used as a marker under hybridisation conditions wherein said polynucleotide or oligonucleotide fails to hybridise to a DNA or RNA encoding an integrin subunit α1.

118. A process according to claim 117, whereby said polynucleotide or oligonucleotide is a polynucleotide or oligonucleotide coding for a peptide chosen from the group comprising peptides of the cytoplasmic domain, the I-domain and the spliced domain.

119. A process according to claim 117, whereby said polynucleotide or oligonucleotide is a polynucleotide or oligonucleotide coding for a peptide comprising the amino acid sequence KLGFFAHKKIPEEEKREEKLEQ.

120. A process according to claim 117, whereby said polynucleotide or oligonucleotide is a polynucleotide or oligonucleotide coding for a peptide comprising the amino

acid sequence from about amino acid no. 952 to about amino acid no. 986 of SEQ ID No. 1.

121. A process according to claim 117, whereby said polynucleotide or oligonucleotide is a polynucleotide or oligonucleotide coding for a peptide comprising the amino acid sequence from about amino acid no. 140 to about amino acid no. 337 of SEQ ID No. 1.

122. A process according to claim 117, whereby said pathological conditions are any pathological conditions involving the integrin subunit α10.

123. A process according to claim 117, whereby said pathological conditions are rheumatoid arthritis, osteoarthrosis or cancer.

124. A process according to claim 117, whereby said pathological conditions are atherosclerosis or inflammation.

125. A process according to any one of claims 117-124, whereby said cells are chosen from the group comprising chondrocytes, smooth muscle cells, endothelial cells, osteoblasts and fibroblasts.

126. A method of using an integrin subunit α10 as defined in claim 1 as a marker or target in transplantation of cartilage or chondrocytes.

127. A method of using binding entities having the capability of binding specifically to an integrin subunit α10 comprising the amino acid sequence shown in SEQ ID No. 1 or SEQ ID No. 2, or an integrin heterodimer comprising said subunit α10 and a subunit β, or to homologues or fragments thereof having essentially the same biological activity, for promoting adhesion of chondrocytes and/or osteoblasts to surfaces of implants to stimulate osseointegration.

128. Use of an integrin heterodimer comprising an integrin subunit α10 and a subunit β, or the subunit α10 thereof, or a homologue or fragment of said integrin or subunit α10 having essentially the same biological activity, as a target for anti-adhesive drugs or

molecules in tendon, ligament, skeletal muscle or other tissues where adhesion impairs the function of the tissue.

129. A method of stimulating, inhibiting or blocking the formation of cartilage or bone, comprising administration to a subject a suitable amount of a pharmaceutical agent or an antibody which is capable of using an integrin heterodimer comprising a subunit α10 and a subunit β, or the subunit α10 thereof, or a homologue or fragment of said integrin or subunit α10 having essentially the same biological activity, as a target molecule.

130. A method of preventing adhesion between tendon/ligaments and the surrounding tissue after infection, inflammation and after surgical intervention where adhesion impairs the function of the tissue, comprising administration to a subject a suitable amount of a pharmaceutical agent or an antibody which is capable of using an integrin heterodimer comprising a subunit α10 and a subunit β, or the subunit α10 thereof, or a homologue or fragment of said integrin or subunit α10 having essentially the same biological activity, as a target molecule.

131. A method of stimulating extracellular matrix synthesis and repair by activation or blockage of an integrin heterodimer comprising a subunit α10 and a subunit β, or of the subunit α10 thereof, or of a homologue or fragment of said integrin or subunit α10 having essentially the same biological activity.

132. A method of using DNA or RNA encoding an integrin subunit α10 or homologues or fragments thereof as a target molecule.

133. A method according to claim 132, whereby a polynucleotide or oligonucleotide hybridises to the DNA or RNA encoding an integrin subunit α10 or homologues or fragments thereof and whereby said polynucleotide or oli-

gonucleotide fails to hybridise to a DNA or RNA encoding en integrin subunit α1.

134. A method of using a human heterodimer integrin comprising a subunit α10 and a subunit β, or the subunit α10 thereof, or a homologue or fragment of said integrin or subunit having essentially the same biological activity, or a DNA or RNA encoding an integrin subunit α10 or homologues or fragments thereof, as a marker or target molecule during angiogenesis.

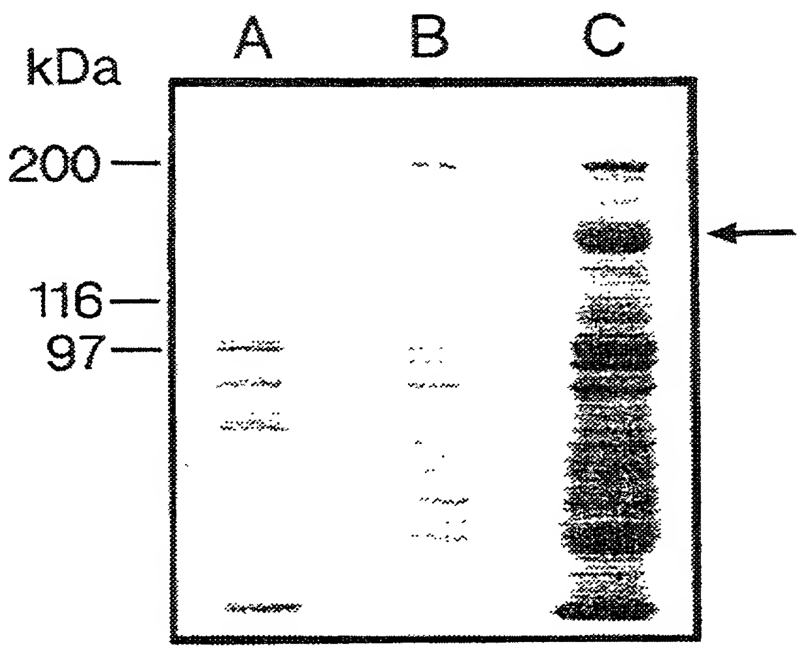

FIGURE 1

Peptide	Amino acid sequence
1	DNTAQTSAYIQYEPHHSI
2	GPGHWDR
3	AAFDGSGQR
4	FAMGALPD
5	FTASLDEWTTAAR
6	VDASFRPQGXLAP

FIGURE 2

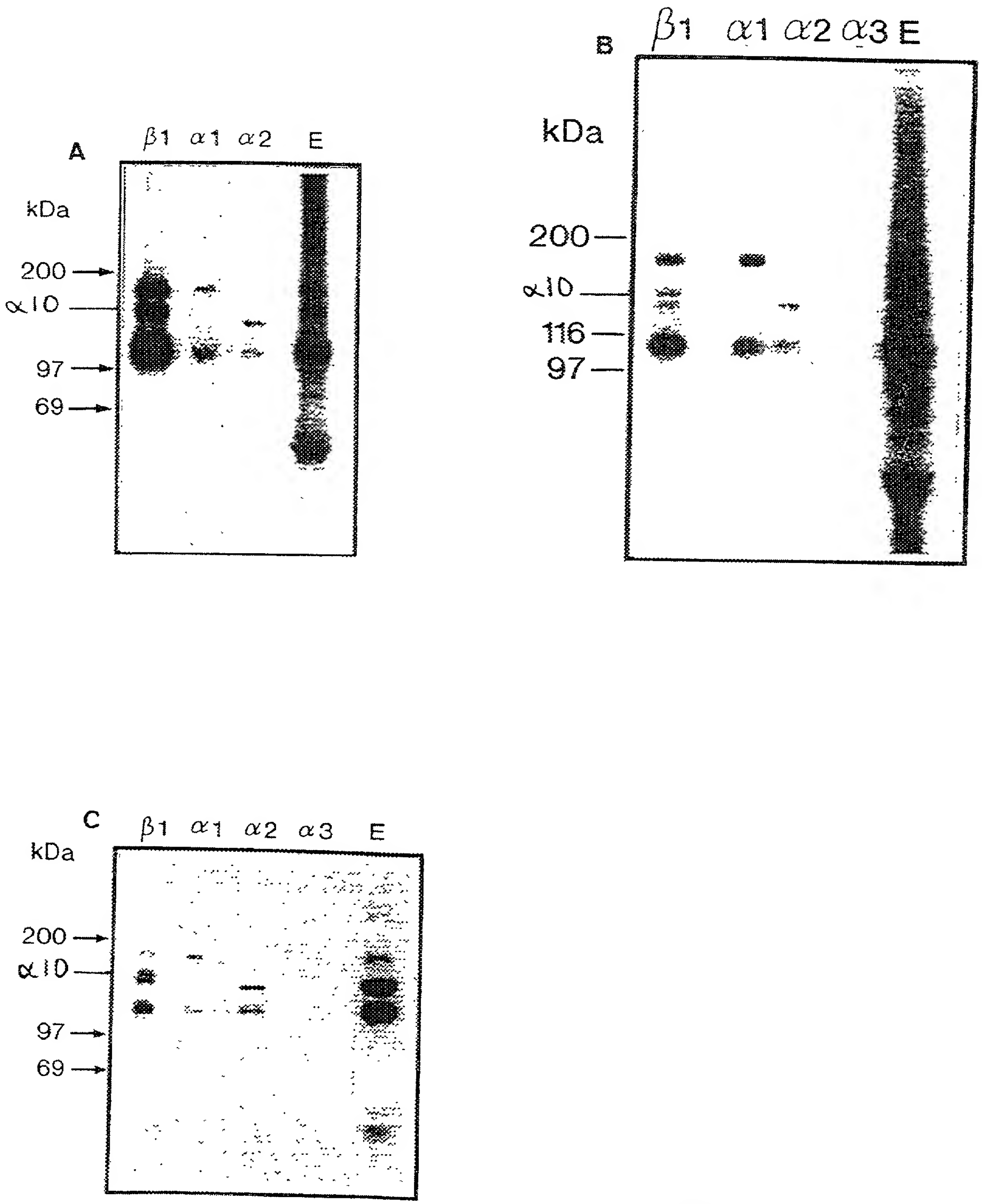
A
β1 α1 α2 E
kDa
200
α10
97
69
B
β1 α1 α2 α3 E
kDa
200
α10
116
97
C
β1 α1 α2 α3 E
kDa
200
α10
97
69

FIGURE 3

900 bp

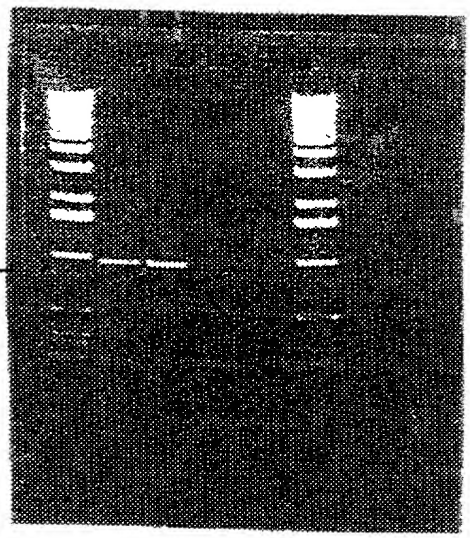

FIGURE 4

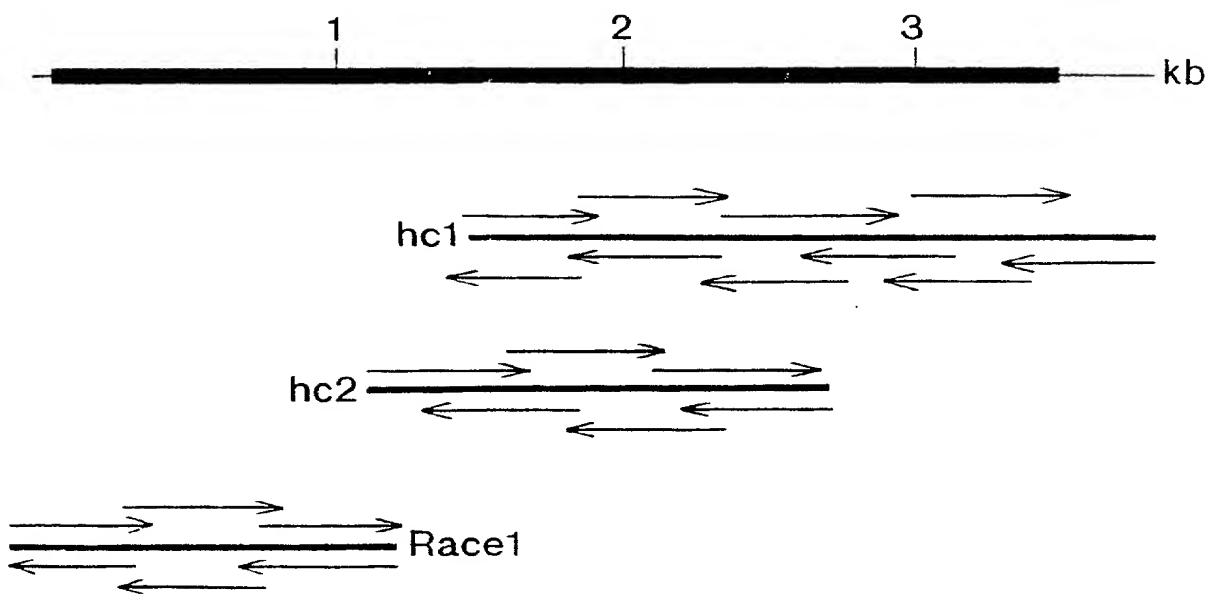

FIGURE 5

CAGGTCAGAAACCGATCAGGCATGGAACTCCCCTTCGTCACTCACCTGTTCTTGCCCCTGGTGTTCCTGACA 72
M E L P F V T H L F L P L V F L T -6

GGTCTCTGCTCCCCCTTTAACCTGGATGAACATCACCCACGCCTATTCCCAGGGCCACCAGAAGCTGAATTT 144
G L C S P F N L D E H H P R L F P G P P E A E F 19

GGATACAGTGTCTTACAACATGTTGGGGGTGGACAGCGATGGATGCTGGTGGGCGCCCCCTGGGATGGGCCT 216
G Y S V L Q H V G G G Q R W M L V G A P W D G P 43

TCAGGCGACCGGAGGGGGGACGTTTATCGCTGCCCTGTAGGGGGGGCCCACAATGCCCCATGTGCCAAGGGC 288
S G D R R G D V Y R C P V G G A H N A P C A K G 67

CACTTAGGTGACTACCAACTGGGAAATTCATCTCATCCTGCTGTGAATATGCACCTGGGGATGTCTCTGTTA 360
H L G D Y Q L G N S S H P A V N M H L G M S L L 91

GAGACAGATGGTGATGGGGGATTCATGGCCTGTGCCCCTCTCTGGTCTCGTGCTTGTGGCAGCTCTGTCTTC 432
E T D G D G G F M A C A P L W S R A C G S S V F 115

AGTTCTGGGATATGTGCCCGTGTGGATGCTTCATTCCAGCCTCAGGGAAGCCTGGCACCCACTGCCCAACGC 504
S S G I C A R V D A S F Q P Q G S L A P T A Q R 139

TGCCCAACATACATGGATGTTGTCATTGTCTTGGATGGCTCCAACAGCATCTACCCCTGGTCTGAAGTTCAG 576
C P T Y M D V V I V L D G S N S I Y P W S E V Q 163

ACCTTCCTACGAAGACTGGTAGGGAAACTGTTTATTGACCCAGAACAGATACAGGTGGGACTGGTACAGTAT 648
T F L R R L V G K L F I D P E Q I Q V G L V Q Y 187

GGGGAGAGCCCTGTACATGAGTGGTCCCTGGGAGATTTCCGAACGAAGGAAGAAGTGGTGAGAGCAGCAAAG 720
G E S P V H E W S L G D F R T K E E V V R A A K 211

AACCTCAGTCGGCGGGAGGGACGAGAAACAAAGACTGCCCAAGCAATAATGGTGGCCTGCACAGAAGGGTTC 792
N L S R R E G R E T K T A Q A I M V A C T E G F 235

AGTCAGTCCCATGGGGGCCGACCCGAGGCTGCCAGGCTACTGGTGGTTGTCACTGATGGAGAGTCCCATGAT 864
S Q S H G G R P E A A R L L V V V T D G E S H D 259

GGAGAGGAGCTTCCTGCAGCACTAAAGGCCTGTGAGGCTGGAAGAGTGACACGCTATGGGATTGCAGTCCTT 936
G E E L P A A L K A C E A G R V T R Y G I A V L 283

GGTCACTACCTCCGGCGGCAGCGAGATCCCAGCTCTTTCCTGAGAGAAATTAGAACTATTGCCAGTGATCCA 1008
G H Y L R R Q R D P S S F L R E I R T I A S D P 307

GATGAGCGATTCTTCTTCAATGTCACAGATGAGGCTGCTCTGACTGACATTGTGGATGCACTAGGAGATCGG 1080
D E R F F F N V T D E A A L T D I V D A L G D R 331

ATTTTTGGCCTTGAAGGGTCCCATGCAGAAAACGAAAGCTCCTTTGGGCTGGAAATGTCTCAGATTGGTTTC 1152
I F G L E G S H A E N E S S F G L E M S Q I G F 355

TCCACTCATCGCCTAAAGGATGGGATTCTTTTTGGGATGGTGGGGGCCTATGACTGGGGAGGCTCTGTGCTA 1224
S T H R L K D G I L F G M V G A Y D W G G S V L 379

TGGCTTGAAGGAGGCCACCGCCTTTTCCCCCCACGAATGGCACTGGAGGACGAGTTCCCCCCTGCACTGCAG 1296
W L E G G H R L F P P R M A L E D E F P P A L Q 403

AACCATGCAGCCTACCTGGGTTACTCTGTTTCTTCCATGCTTTTGCGGGGTGGACGCCGCCTGTTTCTCTCT 1368
N H A A Y L G Y S V S S M L L R G G R R L F L S 427

GGGGCTCCTCGATTTAGACATCGAGGAAAAGTCATCGCCTTCCAGCTTAAGAAAGATGGGGCTGTGAGGGTT 1440
G A P R F R H R G K V I A F Q L K K D G A V R V 451

GCCCAGAGCCTCCAGGGGGAGCAGATTGGTTCATACTTTGGCAGTGAGCTCTGCCCATTGGATACAGATAGG 1512
A Q S L Q G E Q I G S Y F G S E L C P L D T D R 475

GATGGAACAACTGATGTCTTACTTGTGGCTGCCCCCATGTTCCTGGGACCCCAGAACAAGGAAACAGGACGT 1584
D G T T D V L L V A A P M F L G P Q N K E T G R 499

GTTTATGTGTATCTGGTAGGCCAGCAGTCCTTGCTGACCCTCCAAGGAACACTTCAGCCAGAACCCCCCCAG 1656
V Y V Y L V G Q Q S L L T L Q G T L Q P E P P Q 523

GATGCTCGGTTTGGCTTTGCCATGGGAGCTCTTCCTGATCTGAACCAAGATGGTTTTGCTGATGTGGCTGTG 1728
D A R F G F A M G A L P D L N Q D G F A D V A V 547

GGGGCGCCTCTGGAAGATGGGCACCAGGGAGCACTGTACCTGTACCATGGAACCCAGAGTGGAGTCAGGCCC 1800
G A P L E D G H Q G A L Y L Y H G T Q S G V R P 571

CATCCTGCCCAGAGGATTGCTGCTGCCTCCATGCCACATGCCCTCAGCTACTTTGGCCGAAGTGTGGATGGT 1872
H P A Q R I A A A S M P H A L S Y F G R S V D G 595

CGGCTAGATCTGGATGGAGATGATCTGGTCGATGTGGCTGTGGGTGCCCAGGGGGCAGCCATCCTGCTCAGC 1944
R L D L D G D D L V D V A V G A Q G A A I L L S 619

TCCCGGCCCATTGTCCATCTGACCCCATCACTGGAGGTGACCCCACAGGCCATCAGTGTGGTTCAGAGGGAC 2016
S R P I V H L T P S L E V T P Q A I S V V Q R D 643

TGTAGGCGGCGAGGCCAAGAAGCAGTCTGTCTGACTGCAGCCCTTTGCTTCCAAGTGACCTCCCGTACTCCT 2088
C R R R G Q E A V C L T A A L C F Q V T S R T P 667

GGTCGCTGGGATCACCAATTCTACATGAGGTTCACCGCATCACTGGATGAATGGACTGCTGGGGCACGTGCA 2160
G R W D H Q F Y M R F T A S L D E W T A G A R A 691

GCATTTGATGGCTCTGGCCAGAGGTTGTCCCCTCGGAGGCTCCGGCTCAGTGTGGGGAATGTCACTTGTGAG 2232
A F D G S G Q R L S P R R L R L S V G N V T C E 715

CAGCTACACTTCCATGTGCTGGATACATCAGATTACCTCCGGCCAGTGGCCTTGACTGTGACCTTTGCCTTG 2304
Q L H F H V L D T S D Y L R P V A L T V T F A L 739

GACAATACTACAAAGCCAGGGCCTGTGCTGAATGAGGGCTCACCCACCTCTATACAAAAGCTGGTCCCCTTC 2376
D N T T K P G P V L N E G S P T S I Q K L V P F 763

TCAAAGGATTGTGGCCCTGACAATGAATGTGTCACAGACCTGGTGCTTCAAGTGAATATGGACATCAGAGGC 2448
S K D C G P D N E C V T D L V L Q V N M D I R G 787

TCCAGGAAGGCCCCATTTGTGGTTCGAGGTGGCCGGCGGAAAGTGCTGGTATCTACAACTCTGGAGAACAGA 2520
S R K A P F V V R G G R R K V L V S T T L E N R 811

AAGGAAAATGCTTACAATACGAGCCTGAGTATCATCTTCTCTAGAAACCTCCACCTGGCCAGTCTCACTCCT 2592
K E N A Y N T S L S I I F S R N L H L A S L T P 835

CAGAGAGAGAGCCCAATAAAGGTGGAATGTGCCGCCCCTTCTGCTCATGCCCGGCTCTGCAGTGTGGGGCAT 2664
Q R E S P I K V E C A A P S A H A R L C S V G H 859

CCTGTCTTCCAGACTGGAGCCAAGGTGACCTTTCTGCTAGAGTTTGAGTTTAGCTGCTCCTCTCTCCTGAGC 2736
P V F Q T G A K V T F L L E F E F S C S S L L S 883

CAGGTCTTTGGGAAGCTGACTGCCAGCAGTGACAGCCTGGAGAGAAATGGCACCCTTCAAGAAAACACAGCC 2808
Q V F G K L T A S S D S L E R N G T L Q E N T A 907

CAGACCTCAGCCTACATCCAATATGAGCCCCACCTCCTGTTCTCTAGTGAGTCTACCCTGCACCGCTATGAG 2880
Q T S A Y I Q Y E P H L L F S S E S T L H R Y E 931

GTTCACCCATATGGGACCCTCCCAGTGGGTCCTGGCCCAGAATTCAAAACCACTCTCAGGGTTCAGAACCTA 2952
V H P Y G T L P V G P G P E F K T T L R V Q N L 955

GGCTGCTATGTGGTCAGTGGCCTCATCATCTCAGCCCTCCTTCCAGCTGTGGCCCATGGGGGCAATTACTTC 3024
G C Y V V S G L I I S A L L P A V A H G G N Y F 979

CTATCACTGTCTCAAGTCATCACTAACAATGCAAGCTGCATAGTGCAGAACCTGACTGAACCCCCAGGCCCA 3096
L S L S Q V I T N N A S C I V Q N L T E P P G P 1003

CCTGTGCATCCAGAGGAGCTTCAACACACAAACAGACTGAATGGGAGCAATACTCAGTGTCAGGTGGTGAGG 3168
P V H P E E L Q H T N R L N G S N T Q C Q V V R 1027

TGCCACCTTGGGCAGCTGGCAAAGGGGACTGAGGTCTCTGTTGGACTATTGAGGCTGGTTCACAATGAATTT 3240
C H L G Q L A K G T E V S V G L L R L V H N E F 1051

TTCCGAAGAGCCAAGTTCAAGTCCCTGACGGTGGTCAGCACCTTTGAGCTGGGAACCGAAGAGGGCAGTGTC 3312
F R R A K F K S L T V V S T F E L G T E E G S V 1075

CTACAGCTGACTGAAGCCTCCCGTTGGAGTGAGAGCCTCTTGGAGGTGGTTCAGACCCGGCCTATCCTCATC 3384
L Q L T E A S R W S E S L L E V V Q T R P I L I 1099

TCCCTGTGGATCCTCATAGGCAGTGTCCTGGGAGGGTTGCTCCTGCTTGCTCTCCTTGTCTTCTGCCTGTGG 3456
S L W I L I G S V L G G L L L L A L L V F C L W 1123

AAGCTTGGCTTCTTTGCCCATAAGAAAATCCCTGAGGAAGAAAAAAGAGAAGAGAAGTTGGAGCAATGAATG 3528
K L G F F A H K K I P E E E K R E E K L E Q 1145

TAGAATAAGGGTCTAGAAAGTCCTCCCTGGCAGCTTTCTTCAAGAGACTTGCATAAAAGCAGAGGTTTGGGG 3600
GCTCAGATGGGACAAGAAGCCGCCTCTGGACTATCTCCCCAGACCAGCAGCCTGACTTGACTTTTGAGTCCT 3672
AGGGATGCTGCTGGCTAGAGATGAGCCTTTACCTCAGACAAGAAGAGCTGGCACCAAAACTAGCCATGCTCC 3744
CACCCTCTGCTTCCCTCCTCCTCGTGATCCTGGTTCCATAGCCAACACTGGGGCTTTTGTTTGGGGTCCTTT 3816
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FIGURE 6

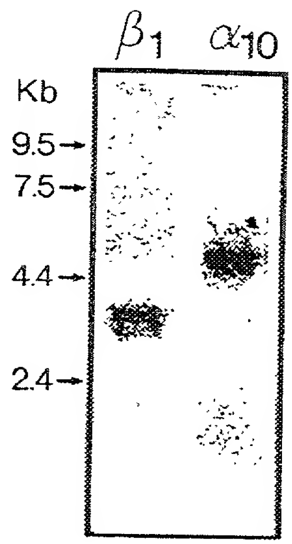
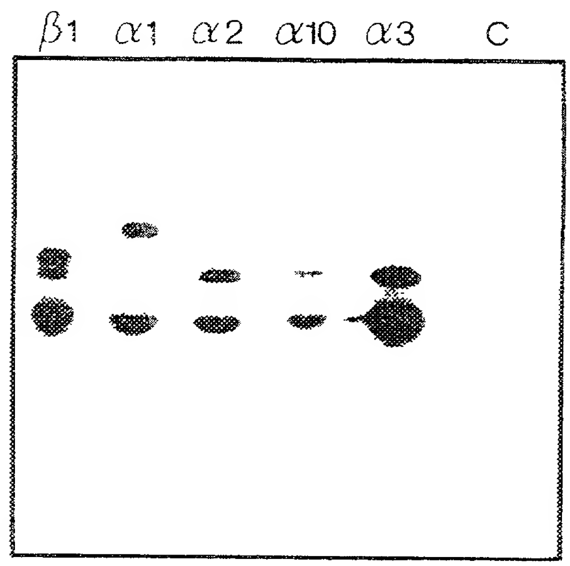


FIGURE 7

A



B

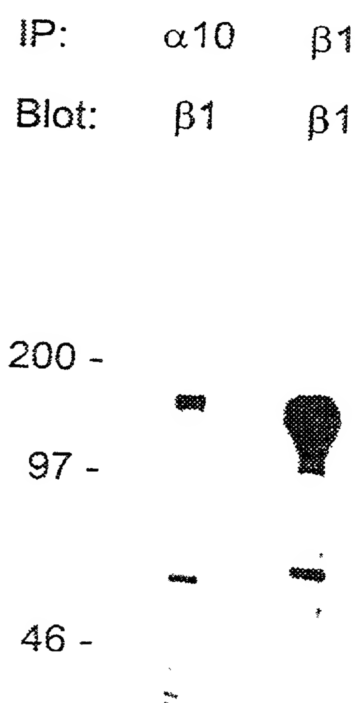


FIGURE 8

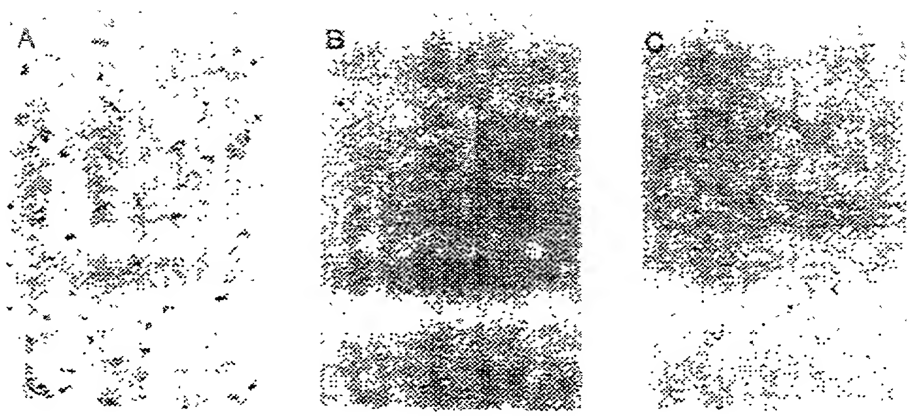


FIGURE 9

A

B

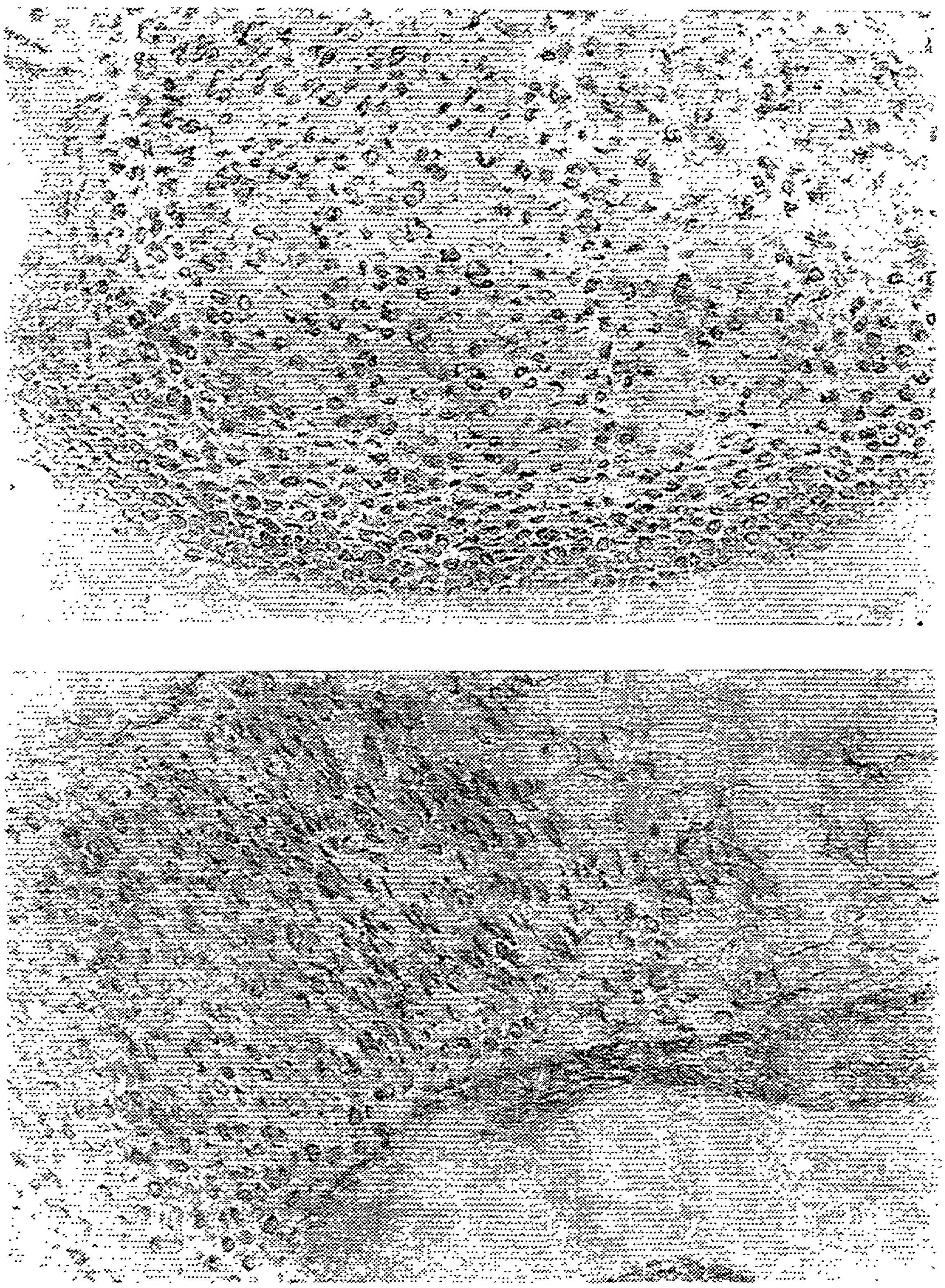
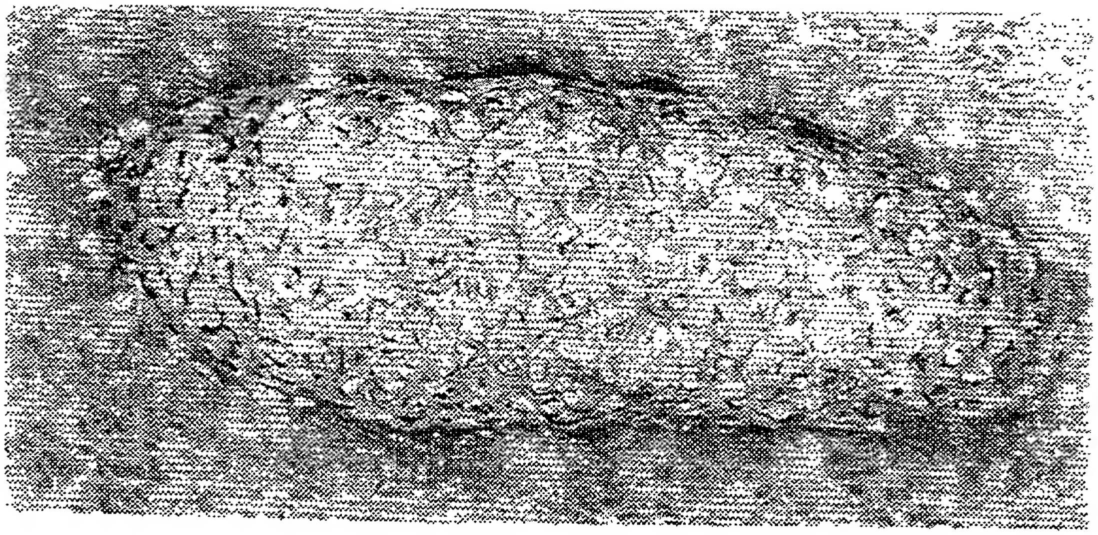
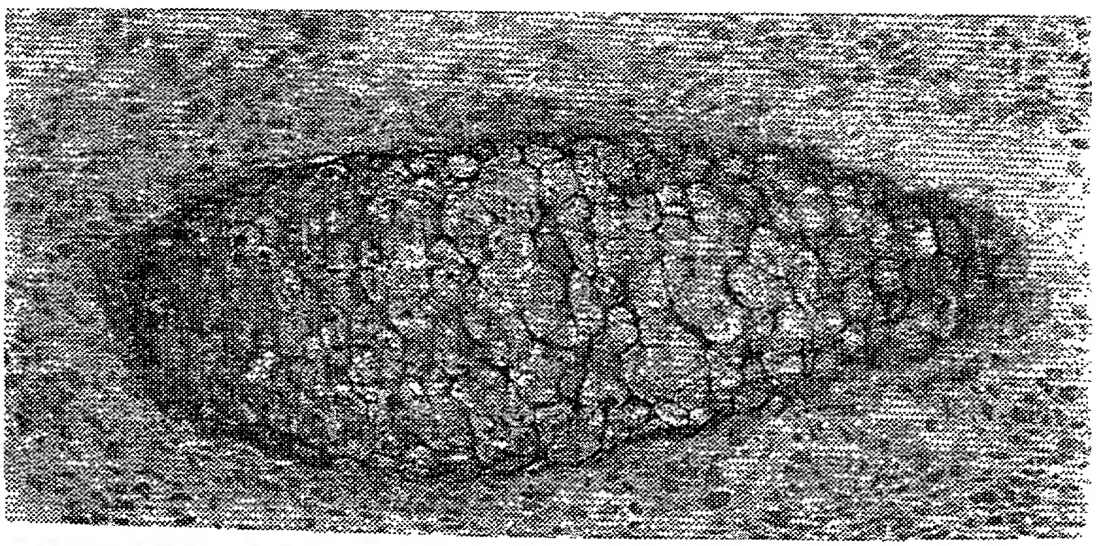


FIGURE 10

A



B



C

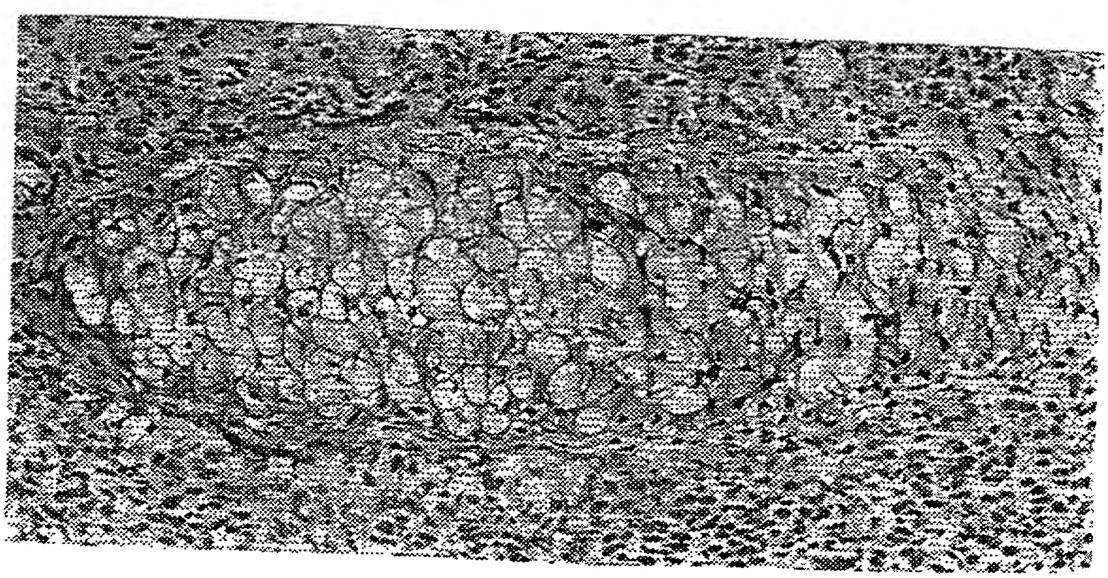


FIGURE 11

Human RNA Master blot

Tissue	α10 expression	Tissue	α10 expression
Aorta	++++	Thyroid gland	-
Trachea	+	Salivary gland	-
Lung	++	Spleen	-
Fetal lung	++	Fetal spleen	-
Kidney	++	Thymus	-
Fetal kidney	(+)	Fetal thymus	-
Heart	(+)	Peripherial leucocyte	-
Fetal heart	++	Lymph node	-
Spinal cord	++	Appendix	-
Mammary gland	(+)	Placenta	-
Bone marrow	(+)	Whole brain	-
Small intestine	(+)	Fetal brain	-
Skeletal muscle	-	Amygdala	-
Liver	-	Caudate nucleus	-
Fetal liver	-	Cerebellum	-
Colon	-	Cerebral cortex	-
Bladder	-	Frontal lobe	-
Uterus	-	Hippocampus	-
Prostate	-	Medulla oblongata	-
Stomach	-	Occipitial lobe	-
Testis	-	Putamen	-
Ovary	-	Substantia nigra	-
Pancreas	-	Temporal lobe	-
Piutiatary gland	-	Thalamus	-
Adrenal gland	-	Subthalamic nucleus	-

FIGURE 12

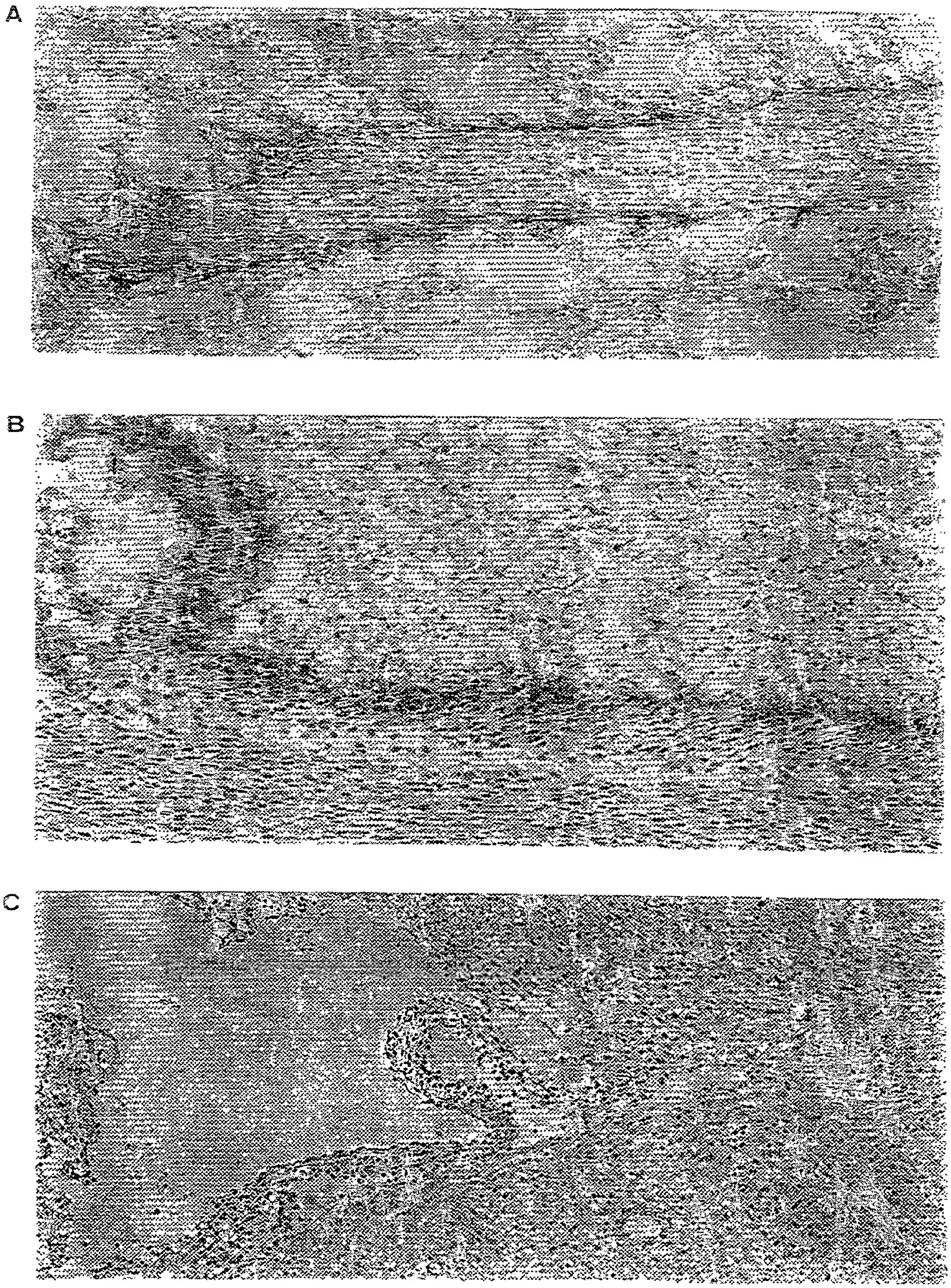


FIGURE 13

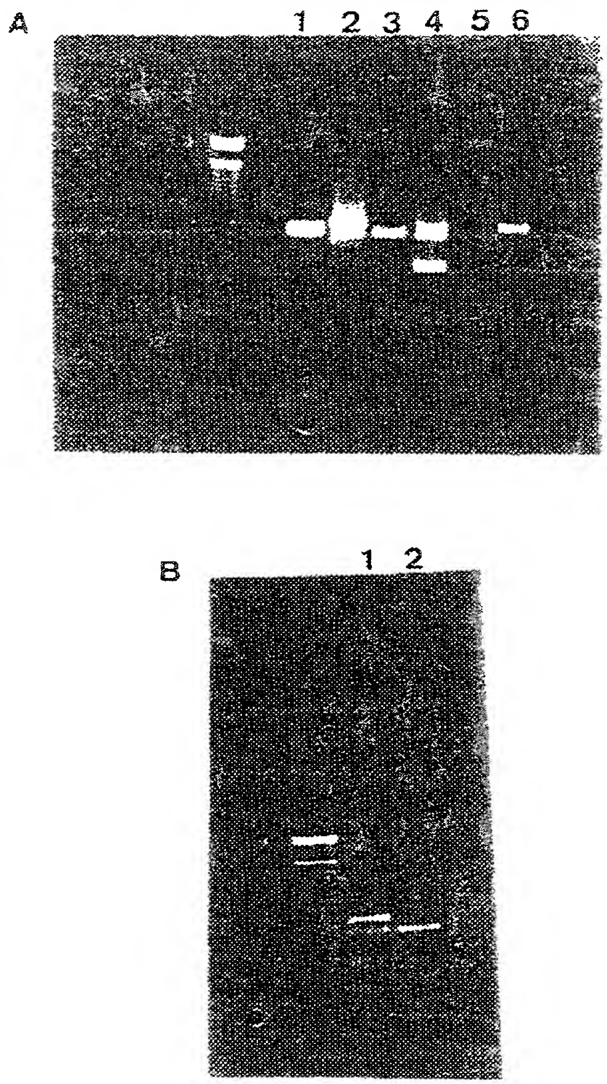


FIGURE 14

```
TGNTMMMKCMCACGAKMGWSAKGNCCGAKGGTKGKGVAAVGTGACARAGCTNGMNAAAARANGAAGTATGACCWGTGGGC 80
 ?  ?  ?  ?  R  ?  ?  ?  P  ?  V  ?  ?  ?  D  ?  A  ?  ?  K  ?  K  Y  D  ?  W  A
  ?  ?  ?  H  ?  ?  ?  ?  R  ?  ?  ?  ?  V  T  ?  L  ?  K  ?  ?  S  M  T  ?  G
V  ?  ?  ?  T  ?  ?  ?  ?  ?  G  ?  ?  ?  .  Q  S  ?  ?  K  ?  E  V  .  P  V  G

CRAGATAGMKAMDAAGCNGMSAGKTRAMGGACGATGGNCCMGCCAAVCGABWGGNAAHTBCGGCNWDCARNGTCCAAATK 160
 ?  I  ?  ?  K  ?  ?  ?  ?  G  R  W  ?  ?  Q  ?  ?  G  ?  ?  G  ?  Q  ?  P  N
P  R  .  ?  ?  S  ?  ?  ?  ?  D  D  G  P  A  ?  R  ?  ?  ?  ?  A  ?  ?  V  Q  ?
 ?  D  ?  ?  ?  A  ?  ?  .  R  T  M  ?  ?  P  ?  ?  ?  ?  ?  R  ?  ?  ?  S  K  ?

SANKTCSCAGGAACCMACGGAMTGGCTCGCARCCCDTAGGGATCAGGKACGATGRCTCSCCGRNSKACTCSGNKTGATWA 240
?  ?  ?  R  N  ?  R  ?  G  S  Q  P  ?  G  I  R  ?  D  ?  S  P  ?  ?  S  ?  .  ?
 ?  ?  ?  G  T  ?  G  ?  A  R  ?  P  .  G  S  G  T  M  ?  ?  R  ?  T  ?  ?  D  ?
  ?  S  Q  E  P  T  ?  W  L  A  ?  ?  R  D  Q  ?  R  ?  L  ?  ?  ?  L  ?  ?  I

ATCGMNWGTMGGMAGGCGGMGGAATTRWAAAGTANTGGTMGAMAKATGWGVMGGAWATGATRRGTMGACTVTMVMGGVAK 320
 I  ?  ?  R  ?  A  ?  E  L  ?  S  ?  G  R  ?  M  ?  R  ?  .  ?  V  D  ?  ?  G  ?
  S  ?  V  G  R  R  R  N  ?  K  V  ?  V  ?  ?  ?  ?  G  ?  D  ?  ?  T  ?  ?  ?
N  R  ?  ?  ?  G  G  G  I  ?  K  ?  W  ?  ?  ?  ?  ?  ?  M  ?  ?  R  L  ?  R  ?

VTAKSGGTACAGGCGAAKACARGRAKGTGTCTGAGGAADTCAGNAGGACAAMMTTGCCGAAGTCMGGACTTAGKATRGAT 400
  ?  ?  Y  R  R  ?  Q  ?  ?  V  .  G  ?  Q  ?  D  ?  ?  A  E  V  R  T  .  ?  ?
?  ?  G  T  G  E  ?  ?  ?  V  S  E  E  ?  ?  R  T  ?  L  P  K  S  G  L  ?  ?  D
 ?  ?  V  Q  A  ?  T  ?  ?  C  L  R  ?  S  ?  G  Q  ?  C  R  S  ?  D  L  ?  ?  I

ACGAANCKTRGATCTTAMADGGGGGNKAGCGAGTGCSTAAACGVARATRGGNSWGTCTACTTMAACNCCAAGNGDGGACA 480
Y  E  ?  ?  I  L  ?  G  G  ?  R  V  ?  K  R  ?  ?  ?  ?  L  L  ?  ?  Q  ?  ?  T
 T  ?  ?  ?  S  ?  ?  G  ?  S  E  C  ?  N  ?  ?  ?  ?  V  Y  ?  N  ?  K  ?  G  H
  R  ?  ?  D  L  ?  ?  G  ?  A  S  A  .  T  ?  ?  G  ?  S  T  ?  T  P  ?  ?  D

TTTACTAGASGAGGAGAGTAGCCAGATCACDTGAGATGATCTAAKGTGGGGTCCCGTTGCCAGTATATGAGAGGACTGGT 560
 F  T  R  ?  G  E  .  P  D  H  ?  R  .  S  ?  V  G  S  R  C  Q  Y  M  R  G  L  V
  L  L  ?  E  E  S  S  Q  I  T  .  D  D  L  ?  W  G  P  V  A  S  I  .  E  D  W
I  Y  .  ?  R  R  V  A  R  S  ?  E  M  I  .  ?  G  V  P  L  P  V  Y  E  R  T  G

TCGGCAGACATWGATGCTCTTTGCTGACTCACATATTGTTGCCVTGAGKATGATCAGATACGATCTGWTGTCCCTCATCA 640
  R  Q  T  ?  M  L  F  A  D  S  H  I  V  A  ?  ?  M  I  R  Y  D  L  ?  S  L  I
F  G  R  H  ?  C  S  L  L  T  H  I  L  L  P  .  ?  .  S  D  T  I  ?  C  P  S  S
 S  A  D  I  D  A  L  C  .  L  T  Y  C  C  ?  E  ?  D  Q  I  R  S  ?  V  P  H  H

TGAATSTGRGCCGTGATGCTAATGAGATTCGCCTATGATGGAACAAGAGACTTMTGCTACAGCAGGCGAATGAAGGTTTC 720
M  N  ?  ?  R  D  A  N  E  I  R  L  .  W  N  K  R  L  ?  L  Q  Q  A  N  E  G  F
 .  ?  ?  A  V  M  L  M  R  F  A  Y  D  G  T  R  D  ?  C  Y  S  R  R  M  K  V  S
  E  ?  ?  P  .  C  .  .  D  S  P  M  M  E  Q  E  T  ?  A  T  A  G  E  .  R  F

TAGAGTAGGAGTCTCAGGAGGAGAGAAACTGTGGACCTGGAGGACCAGGGACTCCAGGAGGAAGTWGCCACAACTGGCTT 800
 .  S  R  S  L  R  R  R  E  T  V  D  L  E  D  Q  G  L  Q  E  E  V  A  T  T  G  L
  R  V  G  V  S  G  G  E  K  L  W  T  W  R  T  R  D  S  R  R  K  ?  P  Q  L  A
L  E  .  E  S  Q  E  E  R  N  C  G  P  G  G  P  G  T  P  G  G  S  ?  H  N  W  L

GMAGTTTCGGCTCCGATCCTGATACWGGCTCGTCCTTVGAGTTATCCCCCTCTCTTGCTGGATGGCTCAGAAATGCCTGG 880
  ?  F  R  L  R  S  .  Y  ?  L  V  L  ?  V  I  P  L  S  C  W  M  A  Q  K  C  L
?  S  F  G  S  D  P  D  T  G  S  S  ?  E  L  S  P  S  L  A  G  W  L  R  N  A  W
 ?  V  S  A  F  I  L  I  ?  A  R  P  ?  S  Y  P  P  L  L  L  D  G  S  E  M  P  G

ACCTTTTCATCCCCACTGGACAAACTAGGCGTCTGGCGTTGTGGCCCTGGGATTGTGGGGCTGTGTGGCCTCATATCCTC 960
D  L  F  I  P  T  G  Q  T  R  R  L  A  L  W  P  W  D  C  G  A  V  W  P  H  I  L
 T  F  S  S  P  L  D  K  L  G  V  W  R  C  G  P  G  I  V  G  L  C  G  L  I  S  S
  P  F  H  P  H  W  T  N  .  A  S  G  V  V  A  L  G  L  W  G  C  V  A  S  Y  P

CATTCTGTCTATTCTCACCCTAATCTGTCCCTGGNTACGACTCAAGCCCYGACTGACAMTGTGGTACAAGATAAGGAGGG 1040
 H  S  V  Y  S  H  P  N  L  S  L  ?  T  T  Q  A  ?  T  D  ?  V  V  Q  D  K  E  G
  I  L  S  I  L  T  L  I  C  P  W  ?  R  L  K  P  ?  L  T  ?  W  Y  K  I  R  R
P  F  C  L  F  S  P  .  S  V  P  G  Y  D  S  S  P  D  .  ?  C  G  T  R  .  G  G

AGCCCAGGTGGGTGAGATGGAAGCTGAGATGGTNCACTGTGTGCCMACCTCATTGTAATTCAACTNCCTTGACTGAAGTT 1120
  A  Q  V  G  E  M  E  A  E  M  V  H  C  V  P  T  S  L  .  F  N  ?  L  D  .  S
E  P  R  W  V  R  W  K  L  R  W  ?  T  V  C  ?  P  H  C  N  S  T  ?  L  T  E  V
 S  P  G  G  .  D  G  S  .  D  G  ?  L  C  A  ?  L  I  V  I  Q  L  P  .  L  K  L

AAAATCCAGATCCYTAGGGATGAGGGGAAGAACCTGCCAAAGACGGGTCAGGAAGGCAGTGCTAAGGGAAGGCTCCTGCA 1200
.  N  P  D  P  .  G  .  G  E  E  F  A  K  D  G  S  G  R  Q  C  .  G  K  A  P  A
 K  I  Q  I  ?  R  D  E  G  K  N  L  P  K  T  G  Q  E  G  S  A  K  G  R  L  L  Q
  K  S  R  S  L  G  M  R  G  R  T  C  Q  R  R  V  R  K  A  V  L  R  E  G  S  C

GGCCTCTGCAGTTGGACTTCATTCAGTCCCATTGCCAGAATCTCATAGCTCTTCCCYYTATCTCTCTGTCTTGAGTCTAG 1280
 G  L  C  S  W  T  S  F  S  P  I  A  R  I  S  .  L  F  P  L  S  L  C  L  E  S  S
  A  S  A  V  G  L  H  S  V  P  L  P  E  S  H  S  S  S  ?  Y  L  S  V  L  S  L
R  P  L  Q  L  D  F  I  Q  S  H  C  Q  N  L  I  A  L  P  ?  I  S  L  S  .  V  .

TTAAGAATTTGTTACCGGAGACAGAATTCTCTTTCTTAGCCTCCTGGCCAGATATTTAAAAGGAGGGGGGTGGGTTACTT 1360
  .  E  F  V  T  G  D  R  I  L  F  L  S  L  L  A  R  Y  L  K  G  G  G  W  V  T
V  K  N  L  L  P  E  T  E  F  S  F  L  A  S  W  P  D  I  .  K  E  G  G  G  L  L
 L  R  I  C  Y  R  R  Q  N  S  L  S  .  P  P  G  Q  I  F  K  R  R  G  V  G  Y  F
```

FIGURE 15a

```
TTTGGTAGGGGAAGCTTAAGTTATGGATAGCAAAGTGCTAATTGTATTCTTTTTTTCTGAAACCTCATGTAGCATTTTTC 1440
F W . G K L K L W I A K C . L Y S F F L K P H V A F F
 F G R G S L S Y G . Q S A N C I L F F . N L M . H F S
  L V G E A . V M D S K V L I V F F F S E T S C S I F

TTCCCTTCCACCCTCCATACTTTCCCAGGCTTCATTTCATGCCCGGCGTCTCTTCGCTCACACCGCTGCAGGCTGTTTGA 1520
 F P S T L H T F P G F I S C P A S L R S H R C R L F E
  S L P P S I L S Q A S F H A R R L F A H T A A G C L
L P F H P P Y F P R L H F M P G V S S L T P L Q A V .

GGCTTCTCCCCTGGGTCTGCCTCAGCAGACTGCCTCCACACTTTCCAGTTTCTGCGTACACGTTGATATTAGAGTTTCCT 1600
 A S P L G L P Q Q T A S T L S S F C V H V D I R V S
R L L P W V C L S R L P P H F P V S A Y T L I L E F P
 G F S P G S A S A D C L H T F Q F L R T R . Y . S F L

TCCCCACTTGGCTCTTGCTCTTTCTCTGACTACCCAGGCTGATGCCATGTCTGGCCTCTTCCTGTAAATACTGTACAATG 1680
F P T W L L L F L . L P R L M F C L A S S C K Y C T M
 S P L G S C S F S D Y P G . C H V W P L P V N T V Q .
  P H L A L A L S L T T Q A D A M S G L F L . I L Y N

ATTCTATGTAAATAACTGGTCCTTGCCCACAGAGCAAGCAAGCCTTCTAGGCTAACAAATTAAAGATCAAGTTTGCTCAC 1760
 I L C K . L V L A H R A S K P S R L T N . R S S L L T
  F Y V N N W S L P T E Q A S L L G . Q I K D Q V C S
D S M . I T G F C P Q S K Q A F . A N K L K I K F A H

TGACTTTTTTATTCAATTCAAGATGGCGGGGGGTGGGGTGGGGGGGCGGATTGCCTGTTTTCACTGTGGTACCTAGGCAG 1840
  D F F I Q F K M A G G G V G G R I A C F H C G T . A
L T F L F N S R W R G V G W G G G L P V F T V V P R Q
 . L F Y S I Q D G G G W G G G A D C L F S L W Y L G R

GGCTGAAGCTCTGAGCTCCCCTGCTTTAGGCTTCTGAGTAGCCTACAGTGAGTGTTACTGTGTCCAGCTGCTCGTTGACA 1920
G L K L . A P L L . A S E . P T V S V T V S S C S L T
 G . S S E L P C F R L L S S L Q . V L L C P A A R . H
  A E A L S S P A L G F . V A Y S E C Y C V Q L L V D

TCTGGTCTCTCATGGTCTGGTCATTGTAAGCCTTAGCTCTCTGACTGTGGATGGCTTTCCTTGGCGTTAGCAGCTAACAT 2000
 S G L S W S G H C K P . L S D C G W L S L A L A A N M
  L V S H G L V I V S L S S L T V D G F P W R . Q L T
I W S L M V W S L . A L A L . L W M A F L G V S S . H

GGTTACAGGATTTCACTGAAAATTTAAATGTTGGGGGAAAGGTGCGGACACACCATAATGGTCCCAATTCAAAACAATCC 2080
 V T G F H . K F K C W G K G A D T P . W S Q F K T I
W L Q D F T E N L N V G G K V R T H H N G P N S K Q S
 G Y R I S L K I . M L G E R C G H T I M V P I Q N N P

GTGAAACAGCCTCAAGTTAGGGGTGAGATGTTTTCAACCAAAGTAATTATCTTGACACCACAAAGCACACCTGTCTACAG 2160
R E T A S S . G . D V F N Q S N Y L D T T K H T C L Q
 V K Q P Q V R G E M F S T K V I I L T P Q S T P V Y R
  . N S L K L G V R C F Q P K . L S . H H K A H L S T

GCAGTGACTCCCCAAAAGCTATTAGACACACAACAAGCATGACCATAACTCAGTGGATTGGCAAGGTCACACAGTAGGAC 2240
 A V T P Q K L L D T Q Q A . P . L S G L A R S H S R T
  Q . L P K S Y . T H N K H D H N S V D W Q G H T V G
G S D S P K A I R H T T S M T I T Q W I G K V T Q . D

TGCCCTTCACACAGTAGGTAGGAAAATGCTGCTGTCACTGCTGTCAGCTGTTATTTTGCATATCCCATGTTAAGATTAAT 2320
  A L H T V G R K M L L S L L S A V I L H I P C . D .
L P F T Q . V G K C C C H C C Q L L F C I S H V K I N
 C P S H S R . E N A A V T A V S C Y F A Y P M L R L I

AAGGCAAAAAAATATTGTCTCTAAGTCCTACTTTCTGTTCCAAACTGGAGGAAATTATTGAATAAATAAACCGTGCATAAA 2400
. G K K Y C L . V L L S V P N W R K L L N K . T V H K
 K A K N I V S K S Y F L F Q T G G N Y . I N K P C I K
  R Q K I L S L S P T F C S K L E E I I E . I N R A .

AGTAGCCTCAGAAAGGGTCAAAATTTGTGTTTTCTTTGAATATTAGCTGAGGCCTCCAGGGGGCAGCACCAAGGTAGAGA 2480
 S S L R K G Q N L C F L . I L A E A S R G Q H Q G R E
  V A S E R V K I C V F F E Y . L R P P G G S T K V E
K . P Q K G S K F V F S L N I S . G L Q G A A P R . R

GCTGGACTAAGGCTGCTCTGTGTTCCTGTCCTGGGCTCCCCACAGCTCCCTTCCACCACCACTCCCATTCCATCCAACTT 2560
  L D . G C S V F L S W A P H S S L P P P L P F H P T
S W T K A A L C S C P G L P T A P F H H H S H S I Q L
 A G L R L L C V P V L G S P Q L P S T T T P I P S N F

TATTTTTAGCTGCCAGTGGGAGGGGGCAGGATAGGAGGGAAAGTAACGAAAACAGCCAAGGAGAGGGACAGAGCAACTCA 2640
L F L A A S G R G Q D R R E S N E N S Q G E G Q S N S
 Y F . L P V G G G R I G G K V T K T A K E R D R A T Q
  I F S C Q W E G A G . E G K . R K Q P R R G T E Q L

GAGCCTCTCGGACTGGACCGGACAAGCGCCCATGGAGTCTCTCTCCATCCCTCACCTGCTCCTGCCCCTGGCGTWGCTGA 2720
 E P L G L D R T S A H G V S L H F S P A P A P G V A D
  S L S D W T G Q A P M E S L S I P H L L L P L A ? L
P A S R T G P D K R P W S L S F S L T C S C P W R ? .
```

FIGURE 15b

```
CAGGTGAGGGAAGCAAACTTGGTTTCTGCTGGGAATGGAAGTTATGTGGATTGTTTATAATTGGGACCATTATGGCTAAA 2800
 R . G K Q T W F L L G M E V M W I V Y N W D H Y G .
T G E G S K L G F C W E W K L C G L F I I G T I M A K
 Q V R E A N L V S A G N G S Y V D C L . L G P L W L K
ATCTYGCGGGCGCTCAGGTCGGAGGTTAATACCGATGCTATATTTCCTGTGTGCACTCATGTTCTTAGACACCCAAATGG 2880
N L A G A Q V G G . Y R C Y I S C V H S C S . T P K W
 I ? R A L R S E V N T D A I F P V C T H V L R H P N G
  S ? G R S G R R L I P M L Y F L C A L M F L D T Q M
CAGTGGCCAAAACTTCCTCTGGCTTGTACCTCATTATCTAAACCTTTGTACCTAATTATCTAAAACCTTGGTCCTAAACT 2960
 Q W P K L P L A C T S L S K P L Y L I I . N L G F K L
  S G Q N F L W L V P H Y L N L C T . L S K T L V L N
A V A K T S S G L Y L I I . T F V P N Y L K P W S . T
CCACAGACATGAGGGCACAGAAAAGAGACGTGTCTCTCATCTTCCATTCGGTTACACTGATTCCTACCTTCCCTGCTTCT 3040
 H R H E G T E K R R V S H L P F G Y T D S Y L P C F
S T D M R A Q K R D V S L I F H S V T L I P T F P A S
 F Q T . G H R K E T C L S S S I R L H . F L P S L L L
CCCTGCCATTGGTGCTCCTTGGTGCCTGAGGCATAATTGCCTTACTATGTGGTCAGAACTCTGGGTTCGCCTAACGACCG 3120
S L P L V L L G A . G I I A L L C G Q N S G F A . R P
 P C H W C S L V P E A . L P Y Y V V R T L G S P N D R
  P A I G A P W C L R H N C L T M W S E L W V R L T T
AGCTACAGTTTCTGGTCTCATAGCCCTGCCAATTTCCTGGATTAAAAAAAAAAGGCTCACATATAAAATACCTTTTCTGA 3200
 S Y S F W S H S P A N F L D . K K K A H I . N T F S E
  A T V S G L I A L P I S W I K K K R L T Y K I P F L
E L Q F L V S . P C Q F P G L K K K G S H I K Y L F .
AAATGAGCACAGTGTGAGTTGAAGTTAGATTTTGGGGGATGGAGGGTTGCTTGGATGCAAAGAGCAAGACAGTAGAGAAG 3280
 N E H S V S . S . I L G D G G L L G C K E Q D S R E
K M S T V . V E V R F W G M E G C L D A K S K T V E K
 K . A Q C E L K L D F G G W R V A W M Q R A R Q . R R
AGAATCATGGGAGGGATAAGAGGCTGGAATTTTTCCCTGCTAGTGCCCTATAATCTTTGTTTCCTAAAATAACAGCTCTG 3360
E N H G R D K R L E F F P A S A L . S L F P K I T A L
 R I M G G I R G W N F S L L V P Y N L C F L K . Q L .
  E S W E G . E A G I F P C . C P I I F V S . N N S S
ATTTTATGGGAATTGGGGTCAGGAGAAAGGAATCAGTAGGCACAGATGGGACCCCAAGCGTGGACTAAAGTTTGAGGAAA 3440
 I L W E L G S G E P N Q . A Q M G P Q A W T K V . G N
  F Y G N W G Q E K G I S R H R W D P K R G L K F E E
D F M G I G V R R K E S V G T D G T P S V D . S L R K
CTATGGGAGTAGGCAAGGGGTGTTTGTAAGGTGGATGAGATGAGGAGATTGTGGTGGGGGGGAGTCTTGGGGGTGATAGG 3520
  Y G S R Q G V F V R W M R . G D C G G G E S W G . .
T M G V G K G C L . G G . D E E I V V G G S L G G D R
 L W E . A R G V C K V D E M R R L W W G G V L G V I G
ACCCTTAACAGGGATAGATGGCAAACTGTGTGTGGGCAGGCCGGTGGTTCCACCCACTTAATTAGCGTTGAGGTTGGCAG 3600
D P . Q G . M A N C V W A G R W F H P L N . R . G W Q
 T L N R D R W Q T V C G Q A G G S T H L I S V E V G R
  P L T G I D G K L C V G R P V V P P T . L A L R L A
GGCTGGAAGGAGCCAGCACTCTCAACCTTGGAGAAAGTGCAAGTGTGACAAGAAGAAACAGAAAGAGGAGACACCCGGGC 3680
 G W K E P A L S T L E K V Q V . Q E E T E R G D T R A
  A G R S Q H S Q P W R K C K C D K K K Q K E E T P G
G L E G A S T L N L G E S A S V T R R N R K R R H P G
AGGGAGCTCCTTGCCATCGTTTCTTCCCATGGCCCTGGCTTTGGGAAGAATTAGGAAAGGGTGGTGACTCTGCATCCTCA 3760
  G S S L P S F L P M A L A L G R I R K G W . L C I L
Q G A P C H R F F P W P W L W E E L G K G G D S A S S
 R E L L A I V S S H G P G F G K N . E R V V T L H P Q
GAAAAGCCCTCTCTCCCTCTTTGGACTCTCGAGGCTTAGAGAGGAGAATGTGTAGGAGGAATGATGTGGAAAGAGTAACT 3840
R K A L S P S L D S R G L E R R M C R R N D V E R V T
 E K P S L P L W T L E A . R G E C V G G M M W K E . L
  K S P L S L F G L S R L R E E N V . E E . C G K S N
TGACCTATCCAGATGTGTCTGTGAATGAGATTTCAGGAATGAGAATGGAAATACAGCTGTGCTTCAGCATGGCCGAGGGC 3920
 . P I Q M C L . M R F Q E . E W K Y S C A S A W P R A
  D L S R C V C E . D F R N E N G N T A V L Q H G R G
L T Y P D V S V N E I S G M R M E I Q L C F S M A E G
CTTAGGATCCCTCACCCCCACCCCACAGGAAGAGAATCATCCAATCATCCCACCTGGGGTTCTGAGGACATGACATTGAC 4000
  L G S L T P T P Q E E N H P I I P F G V L R T . H .
P . D P S P P P H R K R I I Q S S H L G F . G H D I D
 L R I P H P H P T G R E S S N H P T W G S E D M T L T
ACAGAGCAGGAGAGCTGAGATAGAAACACTCCCTCCTGTCTTGTCTCCCACTAAGCCTCACCAGTCCTTCATTAACTGAT 4080
H R A G E L R . K H S L L S C L P L S L T S P S L T D
 T E Q E S . D R N T P S C L V S H . A S P V L H . L I
  Q S R R A E I E T L P P V L S P T K P H Q S F I N .
```

FIGURE 15c

```
TGGTGGATGCTAATTATGATCCTCACCCCTCAGGTCTCTGCTCCCCCTTTAATCTGGATGAACACCACCCACGACTCTTC 4160
 W  W  M  L  I  M  I  L  T  P  Q  V  S  A  P  P  L  I  W  M  N  T  T  H  D  S  S
  G  G  C  .  L  .  S  S  P  L  R  S  L  L  P  L  .  S  G  .  T  P  P  T  T  L
L  V  D  A  N  Y  D  P  H  P  S  G  L  C  S  P  F  N  L  D  E  H  H  P  R  L  F

ACAGGGCCACCAGAGGCCGAATTTGGATACAGTGTCTTACAGCATGTTGGGGGTGGACAGCGATGGTGAGAGGGAAAACA 4240
 Q  G  H  Q  R  P  N  L  D  T  V  S  Y  S  M  L  G  V  D  S  D  G  E  R  E  N
H  R  A  T  R  G  R  I  W  I  Q  C  L  T  A  C  W  G  W  T  A  M  V  R  G  K  T
 T  G  P  P  E  A  E  F  G  Y  S  V  L  Q  H  V  G  G  G  Q  R  W  .  E  G  K  Q

GAGGACCGTGGGATCGGGACTATGCACTCACTGATAAAGGGGAGGACCGGTCCAAGCTGGCCTTTGAAAGTGCCTGGGGC 4320
R  G  P  W  D  R  D  Y  A  L  T  D  K  G  E  D  R  S  K  L  A  F  E  S  A  W  G
 E  D  R  G  I  G  T  M  H  S  L  I  K  G  R  T  G  P  S  W  P  L  K  V  P  G  A
  P  T  V  G  S  G  L  C  T  H  .  .  R  G  G  F  V  Q  A  G  L  .  K  C  L  G

TCCATGACGTCTCATGCACTCTCCCTCTCACTATACTAAGGACCATGCTCACCGGATCTTTATATCCATATTCTCCTTCC 4400
 S  M  T  S  H  A  L  S  L  S  L  Y  .  G  P  C  S  P  D  L  Y  I  H  I  L  L  P
  P  .  R  L  M  H  S  P  S  H  Y  T  K  D  H  A  H  R  I  F  I  S  I  F  S  F
L  H  D  V  S  C  T  L  P  L  T  I  L  R  T  M  L  T  G  S  L  Y  P  Y  S  P  S

AGGATGCTGGTGGGTGCCCCCTGGGATGGGCCATCAGGTGACCGGAGAGGGGATGTTTATCGTTGCTCTATAGGGGGATT 4480
 G  C  W  W  V  P  P  G  M  G  H  Q  V  T  G  E  G  M  F  I  V  A  L  .  G  D
Q  D  A  G  G  C  P  L  G  W  A  I  R  .  P  E  R  G  C  L  S  L  L  Y  R  G  I
 R  M  L  V  G  A  P  W  D  G  F  S  G  D  R  R  G  D  V  Y  R  C  S  I  G  G  F

CCACAGTGCTCCATGTACCAAAGGCCACCTGGGTAAGAAGAAGCCTGACCTTTCCCCTGCTAATTCCTGATGTTGACATC 4560
S  T  V  L  H  V  P  K  A  T  W  V  R  R  S  L  T  F  P  L  L  T  P  D  V  D  I
 P  Q  C  S  M  Y  Q  R  P  P  G  .  E  E  A  .  P  F  P  C  .  F  L  M  L  T  S
  H  S  A  P  C  T  K  G  H  L  G  K  K  K  P  D  L  S  P  A  N  S  .  C  .  H

TAGTAACTCTGACCCCTTGGACCTTGTCTTCAATGACCCTGAACTAAAGAAGCCGAACTATGACCCCATGACTTCATTCT 4640
 .  .  L  .  P  L  G  P  C  L  Q  .  P  .  T  K  E  A  E  L  .  P  H  D  F  I  L
  S  N  S  D  P  L  D  L  V  F  N  D  P  E  L  K  K  P  N  Y  D  P  M  T  S  F
L  V  T  L  T  P  W  T  L  S  S  M  T  L  N  .  R  S  R  T  M  T  P  .  L  H  S

CTTCTACCCTTCCTCCAACCAGGTGACTATCAACTTGGAAATTCCTCTCAGCCTGCTGTGAATATGCACCTAGGGATGTC 4720
  F  Y  P  S  S  N  Q  V  T  I  N  L  E  I  P  L  S  L  L  .  I  C  T  .  G  C
S  S  T  L  P  P  T  R  .  L  S  T  W  K  F  L  S  A  C  C  E  Y  A  P  R  D  V
 L  L  F  F  L  Q  F  G  D  Y  Q  L  G  N  S  S  Q  P  A  V  N  M  H  L  G  M  S

TCTACTAGAGACAGATGCTGATGGGGGATTCATGGTGAGCTGAAAGAAGGGCCTCAGAAGGTTCACAGCAGGGAAGAGAG 4800
L  Y  .  R  Q  M  L  M  G  D  S  W  .  A  E  R  R  A  S  E  G  S  Q  Q  G  R  E
 S  T  R  D  R  C  .  W  G  I  H  G  E  L  K  E  G  P  Q  K  V  H  S  R  E  E  S
  L  L  E  T  D  A  D  G  G  F  M  V  S  .  K  K  G  L  R  R  F  T  A  G  K  R

CATTATGGTATCTGGGCAGTGGTGGCTTGGGCCTTTCATCCCAGTGTTCTGGAGGCAGAGTCAGGCCTGATCTACAGAGT 4880
 H  Y  G  I  W  A  V  V  A  W  A  F  H  P  S  V  L  E  A  E  S  G  L  I  Y  R  V
  I  M  V  S  G  Q  W  W  L  G  P  F  I  P  V  F  W  R  Q  S  Q  A  .  S  T  E
A  L  W  Y  L  G  S  G  G  L  G  L  S  S  Q  C  S  G  G  R  V  R  P  D  L  Q  S

GAGCTCCAGGACAGCCAAGGCTATGCAGAGAAACCCTGTTTTGAAAAACCCAAAACCAAAACTAACCAAACAACAACAAC 4960
  S  S  R  T  A  K  A  M  Q  R  N  P  V  L  K  N  P  K  P  K  L  T  K  Q  Q  Q
 .  A  P  G  Q  P  R  L  C  R  E  T  L  F  .  K  T  Q  N  Q  N  .  P  N  N  N  N
  E  L  Q  D  S  Q  G  Y  A  E  K  P  C  F  E  K  P  K  T  K  T  N  Q  T  T  T  T

AGAAAAAGCACCGTGGTAAGGGAAATTAGTCTGTATAGAAGAGACAAGGAATTCAAAACCCTAGAGAGCAAGGCAGGGTT 5040
Q  K  K  H  R  G  K  G  N  .  S  V  .  K  R  Q  G  I  Q  N  P  R  E  Q  G  R  V
 R  K  S  T  V  V  R  E  I  S  L  Y  R  R  D  K  E  F  K  T  L  E  S  K  A  G  F
  E  K  A  P  W  .  G  K  L  V  C  I  E  E  T  R  N  S  K  F  .  R  A  R  Q  G

CCCCATGGAGTGGTCTCCATCTCTCTTTTAACTAGGTGTGTGTTCCGAGAGGCCCTCTCAAGCCTGGGGATAACTATTTC 5120
  P  H  G  V  V  S  I  S  L  L  T  R  C  V  F  R  E  A  L  S  S  L  G  I  T  I  S
   P  M  E  W  S  P  S  L  F  .  L  G  V  C  S  E  R  P  S  Q  A  W  G  .  L  F
 S  P  W  S  G  L  H  L  S  F  N  .  V  C  V  P  R  G  P  L  K  P  G  D  N  Y  F

TCCTATCCACCCAGGCCTGTGCCCCTCTTTGGTCTCGTGCCTGCGGCAGCTCTGTCTTCAGTTCTGGAATATGTGCCCGT 5200
  P  I  H  P  G  L  C  F  S  L  V  S  C  L  R  Q  L  C  L  Q  F  W  N  M  C  P
L  L  S  T  Q  A  C  A  P  L  W  S  R  A  C  G  S  S  V  F  S  S  G  I  C  A  R
 S  Y  P  P  R  P  V  P  L  F  G  L  V  P  A  A  A  L  S  S  V  L  E  Y  V  P  V

GTGGATGCTTCATTCCGGCCCCAGGGAAGCCTGGCACCCACCGCCCAACGTGAGCCAGTGGAAGGGCCCTGGAAGCTCAG 5280
C  G  C  F  I  P  A  P  G  K  P  G  T  H  R  P  T  .  A  S  G  R  A  L  E  A  Q
 V  D  A  S  F  R  P  Q  G  S  L  A  P  T  A  Q  R  E  P  V  E  G  P  W  K  L  S
  W  M  L  H  S  G  P  R  E  A  W  H  P  P  P  N  V  S  Q  W  K  G  P  G  S  S

TTCCCAGATAGGGATGCTGGGTGGGAAAAACTAGGACAAAGACTTGGTGGAGGGTCTGCATGGCTATCCTCATCATTCCC 5360
  F  P  D  R  D  A  G  W  E  K  L  G  Q  R  L  G  G  G  S  A  W  L  S  S  S  F  P
   S  Q  I  G  M  L  G  G  K  N  .  D  K  D  L  V  E  G  L  H  G  Y  P  H  H  S
V  F  P  .  G  C  W  V  G  K  T  R  T  K  T  W  W  R  V  C  M  A  I  L  I  I  P

AAGTGTGCTTGCAGAAGAGGCTCCTGTTTGCTAACTGATTAGAATTCAGACTCCTTAGGAGAGCCTCAAGACACCAGGAT 5440
  S  V  L  A  E  E  A  P  V  C  .  L  I  R  I  Q  T  P  .  E  S  L  K  T  P  G
Q  V  C  L  Q  K  R  L  L  F  A  N  .  L  E  F  R  L  L  R  R  A  S  R  H  Q  D
 K  C  A  C  R  R  G  S  C  L  L  T  D  .  N  S  D  S  L  G  E  P  Q  D  T  R  I
```

FIGURE 15d

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CTGGTTTTACCAACTTAAAAACAAAACAAAACAGCATATCCTGTGCACAGCCTATCCCTCATCCATCACGTGTCCTCCAT 5520
S G F T N L K T K Q N S I S C A Q P I P H P S R V L H
 L V L P T . K Q N K T A Y P V H S L S L I H H V S S I
  W F Y Q L K N K T K Q H I L C T A Y P S S I T C P P

ATCTTATTTTTGTGGGTCTTATAGATGCCAAGTCAGCACTCAGTTATTGGGTTCTCCCCTCATGCCTTTCATATACTTTC 5600
 I L F L W V L . M P S Q H S V I G F S P H A F H I L S
  S Y F C G S Y R C Q V S T Q L L G S P L M P F I Y F
Y L I F V G L I D A K S A L S Y W V L P S C L S Y T F

TTATCTACTGCCTTTTGGGAGATAGTCTTATGTAGCCCAGGCTGTCCTTGATCTTGGAATTTGCTTGCCTCAGCTTCTCA 5680
  Y L L P F G R . S Y V A Q A V L D L G I C L P Q L L
L I Y C L L G D S L M . P R L S L I L E F A C L S F S
 L S T A F W E I V L C S F G C P . S W N L L A S A S Q

GTCTCAAGTACTGGGATAATAGGCATGCATTGTCTGCCTGGCCTTTGCTGAACATGCCCTCTGTGGCCATTGGTAGGGCA 5760
S L K Y W D N R H A L S A W P L L N M P S V A I G R A
 V S S T G I I G M H C L P G L C . T C P L W P L V G H
  S Q V L G . . A C I V C L A F A E H A L C G H W . G

TGAGTCAAATACTGCCCTCCCCCACAACACACACACAAACGAAAGTGAGGCTCTCTAAGTGTTCCATAGCACAGGGTAGT 5840
 . V K Y C P P P Q H T H K R K . G S L S V P . H R V V
  E S N T A L P H N T H T N E S E A L . V F H S T G .
M S Q I L P S P T T H T Q T K V R L S K C S I A Q G S

GGTAGGCCTCTCGCTAGTGCATATTTCATTCTTTTACTCTGCCCATCTCTTCTTTCTTTGATTTCCACACTGGGGACCTG 5920
  V G L S L V H I S F F Y S A H L F F L . F P H W G F
W . A S R . C I F H S F T L P I S S F F D F H T G D L
 G R P L A S A Y F I L L L C P S L L S L I S T L G T W

GCATAGTACTTTCCTGGTAATTAAGAGAGAATTCCCTTTTAAGTGCCTGCATTGCAGCGTCCTCCTGGGACATTCTCCCT 6000
G I V L S W . L R E N S L L S A C I A A S S W D I L P
 A . Y F P G N . E R I P F . V P A L Q R P P G T F S L
  H S T F L V I K R E F P F K C L H C S V L L G H S F

TGCTGACTACACCCCACATCCTTCCATGTTTTTGTTTCCCATCACTATGCCCCCCTTCTAGGCTGTCCCACATACATGG 6080
 C . L H P T S F H V F C F P S L C P P S R L S H I H G
  A D Y T P H P S M F F V S H H Y A P L L G C P T Y M
L L T T P H I L P C F L F P I T M P P F . A V P H T W

ATGTCGTCATTGTTTTGGATGGCTCCAACAGTATCTATCCCTGGTCAGAAGTTCAGACTTTCCTTCGGAGGCTGGTAGGA 6160
  C R H C F G W L Q Q Y L S L V R S S D F P S E A G R
D V V I V L D G S N S I Y P W S E V Q T F L R R L V G
 M S S L F W M A P T V S I P G Q K F R L S F G G W . E

AGACTGTTCATCGATCCGGAGCAGATACAGGTAAGAGAAAGATATGTGGATAGGATTGGAGGGAAAGAAGTAAACACTCC 6240
K T V H R S G A D T G K R K I C G . D W R E R S K H S
 R L F I D P E Q I Q V R E R Y V D R I G G K E V N T P
  D C S S I R S R Y R . E K D M W I G L E G K K . T L

TGGACCCTTGGATGTAAGCAGCCATGTCCAGCCTCTTGATGACACCCTGGGACATTGTCTTCTACAGAACTCATGCTCAA 6320
 W T L G C K Q P C P A S . . H P G T L S S T E L M L K
  G P L D V S S H V Q P L D D T L G H C L L Q N S C S
L D P W M . A A M S S L L M T P W D I V F Y R T H A Q

GAACTGTGCAATTAACTTACCAAAAAGTCACAAAAATTTCATAATGTTTGAAGTAAGTTTATGATTGTGTGGGGGGCCAC 6400
  N C A I N L P K S H K N F I M F E V S L . L C G G F
R T V Q L T Y Q K V T K I S . C L K . V Y D C V G G H
 E L C N . L T K K S Q K F H N V . S K F M I V W G A T

ACTCAGAGCTTCCCTTTGCTGCTTGTAGTTGCTTGGGCAATGCATGCCATGAGCTGCAAGTTAGACACACCTGTTCACTT 6480
H S E L P F A A C S C L G N A C H E L Q V R H T C S L
 T Q S F P L L L V V A W A M H A M S C K L D T P V H F
  L R A S L C C L . L L G Q C M P . A A S . T H L F T

CCCCTTCATCGTGCTGCAGGTTGGACACACCTGTTAGGGGTTCACTTCCCCTTCATCCTTTGTGCTCCATCTTCTCTACG 6560
 P L H R A A G W T H L L G V H F P F I L C A P S S L R
  P F I V L Q V G H T C . G F T S P S S F V L H L L Y
S P S S C C R L D T P V R G S L P L H P L C S I F S T

CTCTTCATACATCCCATGTGGGCACATGGTCTATTGTTCTCAGGTAGGACTGGTACAGTACGGGGAGAACCCTGTGCATG 6640
  S S Y I P C G H M V Y C S Q V G L V Q Y G E N P V H
A L H T S H V G T W S I V L R . D W Y S T G R T L C M
 L F I H P M W A H G L L F S G R T G T V R G E P C A .

AGTGGTCCCTGGGAGACTTCCGAACAAAGGAAGAAGTTGTGAGAGCAGCAAGGAACCTAAGTCGGAGGGAAGGGCGAGAA 6720
E W S L G D F R T K E E V V R A A R N L S R R E G R E
 S G P W E T S E Q R K K L . E Q Q G T . V G G K G E K
  V V P G R L P N K G R S C E S S K E P K S E G R A R

ACGAGAACCGCCCAAGCGATCATGGTGGCATGGTGAGACATTGTAAAGGGGTCGTGTGAGGGAGGAGGAAGGATCAGCAG 6800
 T P T A Q A I M V A W . D I V K G S C E G G G R I S R
  R E P P K R S W W H G E T L . R G R V R E E E G S A
N E N R P S D H G G M V R H C K G V V . G R R K D Q Q
```

FIGURE 15e

GGAGAGGGAGAGGGTCTGGAGTGTAGTGTATACATCACAAGATGCTCTGGGCGCTTATCTTTATCTGCATGCCAGAAGTT 6880

E R E R V W S V V Y T S Q D A L G A Y L Y L H A R S

G R G R G S G V . C I H H K M L W A L I F I C M P E V

G E G E G L E C S V Y I T R C S G R L S L S A C Q K F

CGTGGAGGAAGGCTAGGTTGCTGTCACCATACTCTCTCTTACTGTATTTGCATTTTATGGTGTCTGTGGGTGTATCTCTC 6960

S W R K A R L L S P Y S L L L Y L H F M V S V G V S L

R G G R L G C C H H T L S Y C I C I L W C L W V Y L S

V E E G . V A V T I L S L T V F A F Y G V C G C I S

CTTGTCTGTTCTGTTTCTGCACACAGAACTCCATCTTTCCTCTTCTACTCCTGCGTCAATTCTGATACCTAGCTTCTCAA 7040

L V C S V S A H R T P S F L F Y S C V N S D T . L L N

L S V L F L H T E L H L S S S T P A S I L I P S F S

P C L F C F C T Q N S I F P L L L L R Q F . Y L A S Q

CCACTCACGCCCTAGTATTCTTTTCAAACATGACTCTAAACCTCTGGGGAGGCTACATGACCTGACTGTCTTTATTCTCC 7120

H S R P S I L F K H D S K P L G R L H D L T V F I L

T T H A L V F F S N M T L N L W G G Y M T . L S L F S

P L T P . Y S F Q T . L . T S G E A T . P D C L Y S P

AGTTCCTTGATCTTGTCAACCCAAGTGTTTGCTGAATGAATCTATAAATAAATAATGCTTGTACATATTTACACTGATGA 7200

Q F L D L V N P S V C . M N L . I N N A C T Y L H . .

S S L I L S T Q V F A E . I Y K . I M L V H I Y T D D

V P . S C Q P K C L L N E S I N K . C L Y I F T L M

CAGATTATTTTATATGTTCCGTGCCATCTAAACAGTCAAGTTGTGACTCTGTGCCAGTTTGCATGCTAGATACTGTTGGG 7280

Q I I L Y V P C H L N S Q V V T L C Q F A C . I L L G

R L F Y M F R A I . T V K L . L C A S L H A R Y C W

T D Y F I C S V P S K Q S S C D S V P V C M L D T V G

GAATGGTGTAGAAGACATCTGACCTCAGTGAACTGCTGACAGTGTTAATACACTATACGGGCATGCCTGCATGCAAGCCT 7360

N G V E D I . P Q . T A D S V N T L Y G H A C M Q A

G M V . K T S D L S E L L T V L I H Y T G M P A C K P

E W C R R H L T S V N C . Q C . Y T I R A C L H A S L

GTGTGTATGTGCATGCATATGCACACACATACATATGACCATATAGCATTCTTTTATCTCTCTTCTTAGCACAGAAGGGT 7440

C V Y V H A Y A H T Y I . P Y S I L L S L F L A Q K G

V C M C M H M H T H T Y D H I A F F Y L S S . H R R V

C V C A C I C T H I H M T I . H S F I S L L S T E G

TCAGTCAGTCCCGGGGGGGACGACCAGAGGCCGCTAGGCTGCTGGTAGTTGTCACTGATGGAGAGTCCCATGATGGAGAG 7520

S V S P G G D D Q R P L G C W . L S L M E S P M M E R

Q S V P G G T T R G R . A A G S C H . W R V P . W R

E S Q S R G G R P E A A R L L V V V T D G E S H D G E

GAACTTCCAGCAGCGCTAAAGGCCTGTGAGGCTGGCAGAGTGACACGTTATGGATTGCGGTGAGACTTGATCAAGTCCA 7600

N F Q Q R . R P V R L A E . H V M G L R . D L I K S

G T S S S A K G L . G W Q S D T L W D C G E T . S S P

E L P A A L K A C E A G R V T R Y G I A V R L D Q V Q

GTTGTTTTGTTTTGTGTTGTATCGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTATGTGTGATAT 7680

S C F V L C C I V C V C V C V C V C V C V C V Y V . Y

V V L F C V V S C V C V C V C V C V C V C V C M C D M

L F C F V L Y R V C V C V C V C V C V C V C V I

GTGTGCATGCATCAGTGCACATACCATAGTGTGTATATGCGGGTCAGAGAACAACCTCAGATGTTGGTCCTCACCTTCCA 7760

V C M H Q C T Y H S V Y M R V R E Q P Q M L V L T F H

C A C I S A H T I V C I C G S E N N L R C W S S P S

C V H A S V H I F . C V Y A G Q R T T S D V G P H L P

TCTTGTTCCAAACTGGATATCTTGTTCACTTCGGCATACAATAAGCCAGATTAGCTGACCCACAAGTCTTGGCAGGTCT 7840

L V P N W I S C S L R H T I S Q I S . P T S L G Q V

I L F Q T G Y L V H F G I Q . A R L A D P Q V L G R S

S C S K L D I L F T S A Y N K P D . L T H K S W A G L

TCTGTCTCAGCCTCCTGTCTCTTGGTTTGAGGCATTCTGGAATTTACAGATAAGCTTGATATCGAATTCCTGCAGCCCGG 7920

F C L S L L S L G L R H S G I Y R . A . Y R I P A A R

S V S A S C L L V . G I L E F T D K L D I E F L Q P G

L S Q P P V S W F E A F W N L Q I S L I S N S C S P

GGGATCCACTAGTTCTAGAGCGGCCGCCACCAAGGGAG 7958

G I H . F . S G R H Q G S

G S T S S R A A A T K G

G D P L V L E R P P P R E

FIGURE 15f

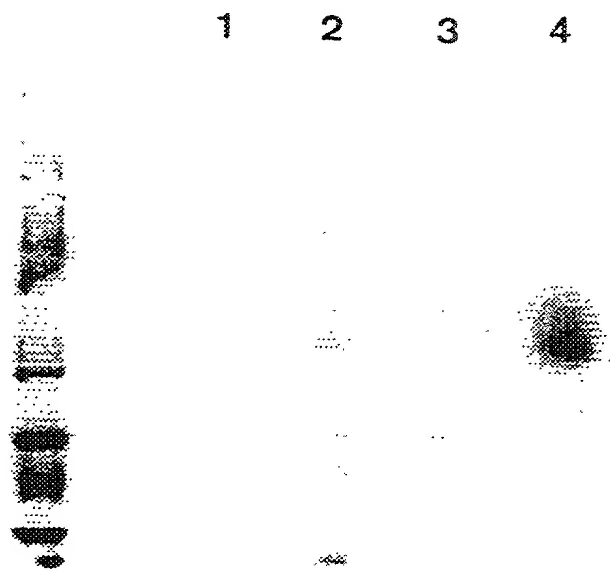

FIGURE 16

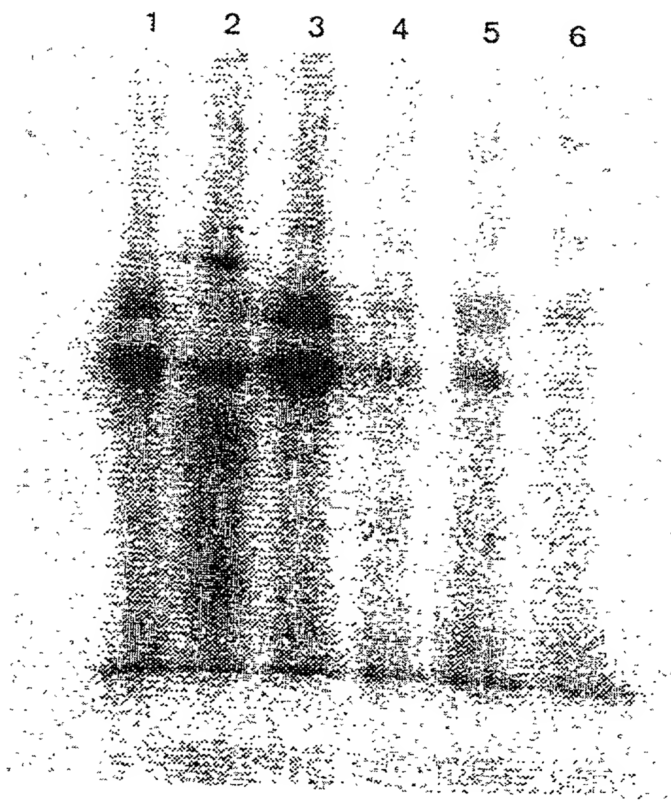

FIGURE 17

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (Includes Reference to Provisional and PCT International Applications)	Attorney's Docket No. 003300-685

As a below named inventor, I hereby declare that:
My residence, post office address and citizenship are as stated below next to my name;
I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

An integrin heterodimer and a subunit thereof

the specification of which (check only one item below):

☐ is attached hereto.

☒ was filed as United States application
Number ______
on 2 October 2000
and was amended
on ______ (if applicable).

☐ was filed as PCT international application
Number ______
on ______
and was amended
on ______ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 (a)-(e) of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. §119:

COUNTRY (if PCT, indicate "PCT")	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 U.S.C. §119
Sweden	9801164-6	2 April 1998	X Yes _No
Sweden	9900319-6	28 January 1999	X Yes _No
			_Yes _No
			_Yes _No

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below.

______ (Application Number) ______ (Filing Date)

______ (Application Number) ______ (Filing Date)

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COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (CONTINUED) (Includes Reference to Provisional and PCT International Applications)	Attorney's Docket No. 003300-685

I hereby claim the benefit under Title 35, United States Code, §120 of any United States applications(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose to the Office all information known to me to be material to the patentability as defined in Title 37, Code of Federal Regulations §1.56, which became available between the filing date of the prior application(s) and the national or PCT international filing date of this application:

PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. 120:

U.S. APPLICATIONS			STATUS *(check one)*		
U.S. APPLICATION NUMBER	U.S. FILING DATE		PATENTED	PENDING	ABANDONED
PCT APPLICATIONS DESIGNATING THE U.S.					
PCT APPLICATION NO.	PCT FILING DATE	U.S. APPLICATION NUMBERS ASSIGNED (if any)			
PCT/SE99/00544	31 March 1999				

I hereby appoint the following attorneys and agent(s) to prosecute said application and to transact all business in the Patent and Trademark Office connected therewith and to file, prosecute and to transact all business in connection with international applications directed to said invention:

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (CONTINUED)
(Includes Reference to Provisional and PCT International Applications)

ATTORNEY'S DOCKET NO.
003300-685

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(05/98